Expert CONSULT

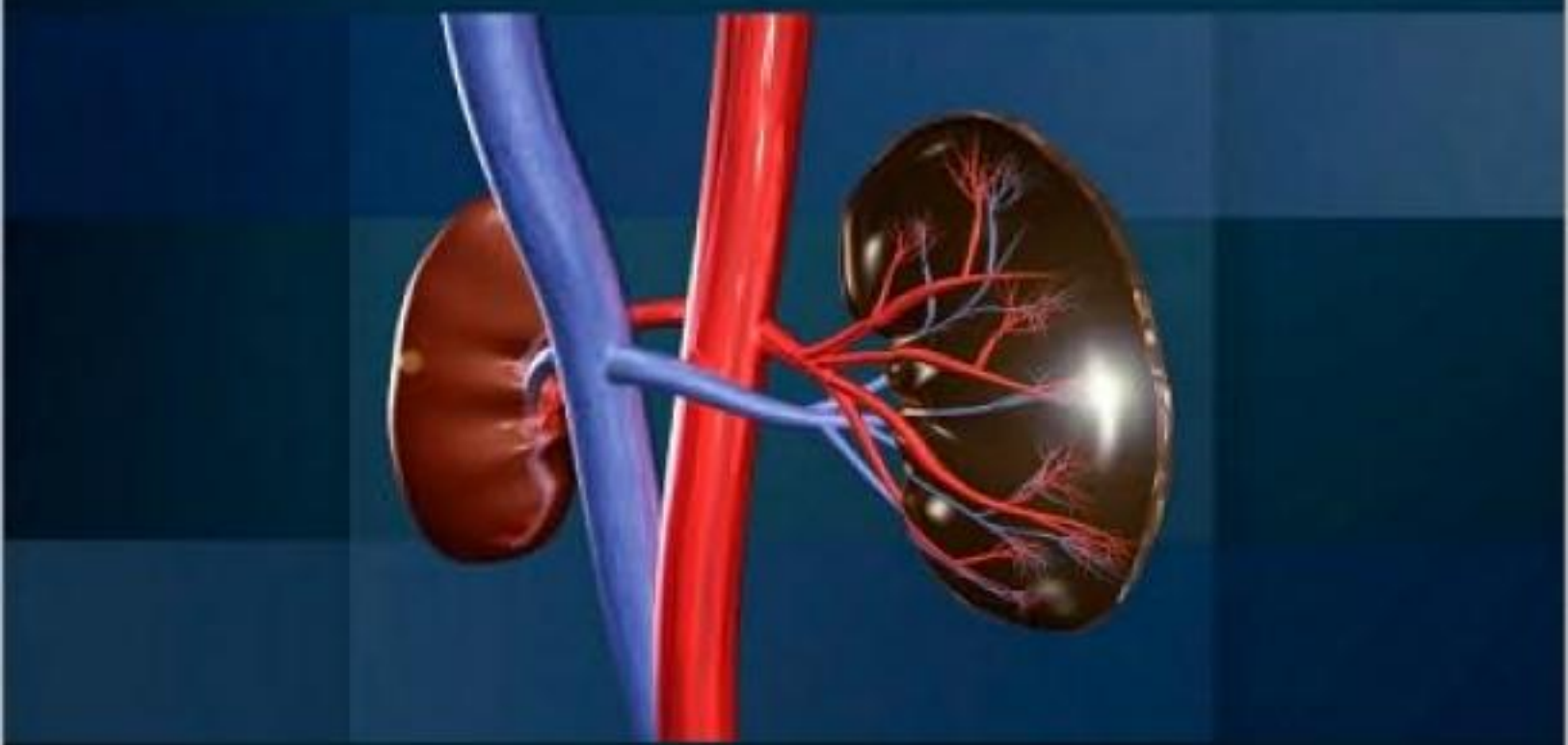
Activate at expertconsult.com

Searchable Full Text Online

Jonathan Himmelfarb Mohamed H. Sayegh

Chronic Kidney Disease, Dialysis, and Transplantation

A Companion to Brenner & Rector's The Kidney



SAUNDERS
ELSEVIER

Chronic Kidney Disease, Dialysis, and Transplantation

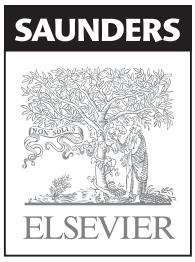
Chronic Kidney Disease, Dialysis, and Transplantation

Companion to Brenner & Rector's The Kidney

Third Edition

Jonathan Himmelfarb, MD
Professor of Medicine
Joseph W. Eschbach Endowed Chair for Kidney Research
Director, Kidney Research Institute
Department of Medicine, Division of Nephrology
University of Washington
Seattle, WA

Mohamed H. Sayegh, MD, FAHA, FASN, ASCI, AAP
Raja N. Khuri Dean, Faculty of Medicine, American University of Beirut
Director, Schuster Family Transplantation Research Center Brigham
Women's Hospital & Children's Hospital, Boston
Visiting Professor of Medicine and Pediatrics, Harvard Medical School
Boston, MA



SAUNDERS
ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

Chronic Kidney Disease, Dialysis, and Transplantation ISBN: 978-1-4377-0987-2

Third Edition

Library of Congress Cataloging-in-Publication Data

Chronic kidney disease, dialysis, and transplantation : companion to Brenner & Rector's the kidney / [edited by] Jonathan Himmelfarb, Mohamed H. Sayegh. – 3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4377-0987-2
1. Hemodialysis. 2. Kidneys–Transplantation. I. Himmelfarb, Jonathan. II. Sayegh, Mohamed H. III. Brenner & Rector's the kidney.
[DNLM: 1. Renal Dialysis. 2. Kidney Failure, Chronic–complications. 3. Kidney Failure, Chronic–therapy. 4. Kidney Transplantation. WJ 378 C55675 2011]
RC901.7.H45D5226 2011
616.6'1–dc22

2009050616

Acquisitions Editor: Kate Dimock
Developmental Editor: Taylor Ball
Publishing Services Manager: Hemamalini Rajendrababu
Project Manager: Nayagi Athmanathan
Design Direction: Steven Stave
Illustrations Manager: Lesley Frazier
Marketing Manager: Abigail Swartz

Printed in United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To my wonderful wife, Deborah, and children, Sarah, Rachel, and Joshua, for their love, support, and guidance.

—JH

To my precious daughter, Layal, and my amazing son, Malek.

—MHS

PREFACE

Chronic Kidney Disease, Dialysis in Transplantation is a companion to *Brenner and Rector's The Kidney.* This 3rd edition is designed to provide a comprehensive and systematic review of the latest available information concerning patho-biology, clinical consequences and therapeutics over a wide spectrum of clinically important kidney diseases. The pace of acquisition of new knowledge in kidney disease is fast and furious, and our goal is to bring a thoughtful, well organized exposition of this burgeoning knowledge base to the readers. To accomplish this we are pleased to have been able to assemble a leading panel of expert contributors who have been challenged to summarize state of the art knowledge in each chapter of the book.

Compared to previous editions, the number of chapters in each section has been expanded and every chapter in this edition has been thoroughly revised and updated. New chapters have been created to cover topics of emerging importance such as chronic kidney disease in the elderly, pharmacoepidemiology in kidney disease, utilization and outcomes of peritoneal dialysis, and biomarkers in acute kidney injury. It is our hope that the reader of these and other chapters will become acquainted with the latest thinking in some of the most important topics in kidney disease. Thus the book is designed to be both a reference source and a practical guide to the clinical management of most major kidney diseases. The text should prove useful and valuable to clinicians, educators and investigators alike.

We wish to thank Barry M. Brenner for his confidence in allowing us to edit this companion volume to the comprehensive accounting of kidney disease found in Brenner and Rector's The Kidney. We also wish to acknowledge the logistical and practical support we received from Ms. Adrianne Brigido and Taylor Ball, who played major roles in the preparation of this new edition for publication. We would particularly like to thank the section editors (Ann O'Hare, Katherine Tuttle, John Stivelman, Rajnish Mehrotra, John Vella, Anil Chandraker, and Sushrut Waikar) for their tremendous contribution in the editing of each chapter, and for working in close conjunction with the chapter authors. Their intellectual rigor and enthusiasm have dramatically influenced the content of this book. We also wish to thank each author for taking considerable time and effort to ensure that each chapter provides state of the art information. We hope that readers achieve the same level of acquisition of new knowledge and enjoyment as we have attained by editing this book.

SECTION EDITORS

Anil Chandraker, MD, FRCP
Assistant Professor of Medicine, Harvard Medical School; Medical Director of Kidney Transplantation, Renal Division, Brigham and Women's Hospital, Brigham and Women's Hospital, Boston, MA
Section V: Transplantation

Rajnish Mehrotra, MD, FACP, FASN
Associate Professor of Medicine, David Geffen School of Medicine, University of California, Los Angeles; Director, Peritoneal Dialysis Program, Harbor-UCLA Medical Center, Torrance, CA
Section IV: Peritoneal Dialysis

Ann M. O'Hare, MA, MD
Associate Professor, Division of Nephrology, Department of Medicine, University of Washington; Staff Physician, VA Puget Sound Healthcare System, Seattle, WA
Section I: Chronic Kidney Disease

John C. Stivelman, MD
Chief Medical Officer, Northwest Kidney Centers, Professor of Medicine, Division of Nephrology, University of Washington School of Medicine, Seattle, WA
Section III: Hemodialysis

Katherine R. Tuttle, MD, FASN, FACP
Medical and Scientific Director, Providence Medical Research, Center Sacred Heart Medical Center, Spokane, WA; Clinical Professor of Medicine, Division of Nephrology, University of Washington School of Medicine, Spokane and Seattle, WA
Section II: Complications and Management of Chronic Kidney Disease

John P. Vella, MD, FRCP, FACP, FASN
Associate Professor, Department of Medicine, Tufts University School of Medicine; Director of Transplantation, Department of Medicine/Nephrology/Transplant, Maine Medical Center, Portland, ME
Section V: Transplantation

Sushrut S. Waikar, MD, MPH
Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Renal Division, Brigham and Women's Hospital, Boston, MA
Section VI: Acute Kidney Injury

LIST OF CONTRIBUTORS

Matthew K. Abramowitz, MD, MS
Assistant Professor of Medicine and Epidemiology & Population Health, Department of Medicine, Epidemiology & Population Health, Albert Einstein College of Medicine; Attending Physician, Department of Medicine, Montefiore Medical Center, Bronx, NY
The Pathophysiology of Uremia

Stuart Abramson, MD, MPH
Clinical Assistant Professor, Tufts University School of Medicine, Boston, MA; Medical Director, Center for Dialysis & Hemotherapeutics, Department of Medicine, Division of Nephrology, Maine Medical Center, Portland, ME
Extracorporeal Treatment of Poisonings

M. Javeed Ansari, MD
Assistant Professor of Medicine, Medicine, Division of Nephrology, Comprehensive Transplant Center, Northwestern University, Feinberg School of Medicine, Chicago, IL
Novel Diagnostics in Transplantation

Matthew J. Arduino, MS, Dr PH
Research Microbiologist, Acting Chief Clinical and Environmental Microbiology Branch, Div Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA
Hemodialysis-associated Infections

George L. Bakris, MD
Professor Medicine, Director, Hypertensive Diseases Unit, Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, IL
Hypertensive Kidney Disease

Rasheed Abiodun Balogun, MD
Associate Professor of Medicine, Division of Nephrology, Department of Medicine, University of Virginia, Charlottesville, VA
Pharmacological Interventions in Acute Kidney Injury

Joanne M. Bargman, MD, FRCPC
Professor of Medicine, Faculty of Medicine, University of Toronto; Staff Nephrologist, Department of Medicine, University Health Network, Toronto, Ontario, Canada
Non-infectious Complications of Peritoneal Dialysis

Monica C. Beaulieu, MD, FRCPC, MHA
Clinical Assistant Professor, Department of Nephrology and Internal Medicine, University of British Columbia, Vancouver, BC, Canada
The Role of the Chronic Kidney Disease Clinic

Jeffrey S. Berns, MD
Professor of Medicine and Pediatrics, Department of Renal-Electrolyte and Hypertension Division, University of Pennsylvania School of Medicine, Philadelphia, PA
Anemia in Chronic Kidney Disease

Peter G. Blake, MB, FRCPC, FRCPI
Professor of Medicine, University of Western Ontario, Chair of Nephrology, London Health Sciences Center, London, Ontario, Canada
Peritoneal Dialysis Prescription and Adequacy

Joseph V. Bonventre, MD, PhD
Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA
Acute Kidney Injury: Biomarkers from Bench to Bedside

Steven M. Brunelli, MD, MSCE
Assistant Professor, Harvard Medical School; Renal Division, Brigham and Women's Hospital, Boston, MA
Anemia in Chronic Kidney Disease

Marilia Cascalho, MD, PhD
Professor of Surgery and Professor of Microbiology and Immunology, Transplantation Biology; Associate Professor of Surgery and Associate Professor of Microbiology & Immunology, Transplantation Biology, University of Michigan, Ann Arbor, MI
Emerging Strategies in Kidney Transplantation

Vimal Chadha, MD
Assistant Professor of Pediatrics, Chair, Section of Nephrology, Virginia Commonwealth University Medical Center, Richmond, VA
The Pediatric Patient with Chronic Kidney Disease

Glenn M. Chertow, MD, MPH
Professor of Nephrology, Stanford School of Medicine, Stanford, CA
Dialytic Management for Acute Renal Failure

Alfred K. Cheung, MD
Professor of Medicine, Department of Medicine, University of Utah; Staff Physician, Department of Medical Service, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT
Hemodialysis Adequacy

Yi-Wen Chiu, MD
Assistant Professor, Department of Renal Care; Attending Physician, Department of Nephrology, Kaohsiung Medical University, Kaohsiung, Taiwan
The Utilization and Outcome of Peritoneal Dialysis

Szeto Cheuk Chun, MD, FRCP
Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China
Peritoneal Dialysis-related Infections

Josef Coresh, MD, MHS, PhD
Professor, Department of Epidemiology, Biostatistics and Medicine, Johns Hopkins University; Faculty, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD
Chronic Kidney Disease: Definition, Epidemiology, Cost and Outcomes

Daniel Cukor, PhD
Assistant Professor of Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY
Depression and Neurocognitive Function in Chronic Kidney Disease

Bruce F. Culleton, MD, FRCPC
Adjunct Associate Professor, Department of Medicine, University of Calgary, Calgary, Alberta, Canada; Senior Medical Director, Renal Division, Baxter Healthcare Corporation, McGaw Park, IL
Hemodialysis Adequacy

Bryan M. Curtis, MD, FRCPC
Memorial University of Newfoundland, St. John's, NL, Canada
The Role of the Chronic Kidney Disease Clinic

Gabriel Danovitch, MD
Professor of Medicine, Department of Medicine, Division of Nephrology, David Geffen School of Medicine at UCLA; Ronald Reagan Medical Center at UCLA, Kidney and Pancreas Transplant Program, Los Angeles, CA
Diagnosis and Therapy of Graft Dysfunction

Simon J. Davies, MD
Professor of Nephrology and Dialysis Medicine, Institute of Science and Technology in Medicine, Keele University; Consultant Nephrologist, Department of Nephrology, University Hospital of North Staffordshire, Stoke-on-Trent, UK
Peritoneal Dialysis Solutions

Ian H. de Boer, MD, MS
Assistant Professor of Medicine, Division of Nephrology, University of Washington, Seattle, WA
Vitamin D Deficiency

Laura M. Dember, MD
Associate Professor of Medicine, Boston University School of Medicine, Boston, MA
Vascular Access

Thomas A. Depner, MD
Professor of Medicine, Division of Nephrology, Department of Medicine, University of California, Davis, Sacramento, CA
Principles Of Hemodialysis

Bradley S. Dixon, MD
Associate Professor, Department of Internal Medicine, University of Iowa; Staff Physician, Internal Medicine, University of Iowa Hospitals and Clinics; Staff Physician, Department of Medicine, Veterans Affairs Medical Center, Iowa City, IA
Vascular Access

Martin S. Favero, PhD
Director of Scientific Affairs, Advanced Sterilization Products, Irvine, CA
Hemodialysis-associated Infections

John S. Gill, MD, FRCPC, MS
Associate Professor of Medicine and Transplant Fellowship Director, Division of Nephrology, Department of Medicine; Associate Professor of Medicine and Transplant Nephrologist, Division of Nephrology, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada
Chronic Kidney Disease and the Kidney Transplant Recipient

Mónica Grafals, MD
Medical Director Pancreas Transplant, Lahey Clinic Medical Center
Assistant Professor, Tufts University
Noninfectious Complications in After Kidney Transplantation

Simin Goral, MD
Associate Professor of Medicine, Department of Medicine: Renal, Electrolyte, and Hypertension Division, University of Pennsylvania, Philadelphia, PA
Current and Emerging Maintenance Immunosuppressive Therapy

Ziv Harel, MD, FRCPC
Department of Medicine, Division of Nephrology, University of Toronto; University Health Network, Toronto, Ontario, Canada
Non-infectious Complications of Peritoneal Dialysis

William E. Harmon, MD
Harvard Medical School, Children's Hospital Boston, Division of Nephrology, Boston, MA
Pediatric Renal Transplantation

Olof Heimbürger, MD, PhD
Associate Professor, Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet; Senior Consultant, Department of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden
Peritoneal Physiology

J. Harold Helderman, MD
Professor of Medicine, Microbiology & Immunology, Department of Internal Medicine; Medical Director Vanderbilt Transplant Center; Chief, Renal Transplant Medicine, Vanderbilt University School of Medicine, Nashville, TN
Current and Emerging Maintenance Immunosuppressive Therapy

Thomas H. Hostetter, MD
Professor, Department of Medicine; Director, Division of Nephrology, Albert Einstein College of Medicine; Director, Division of Nephrology, Montefiore Medical Center, Bronx, NY
The Pathophysiology of Uremia

Cindy Huang, MD, PhD
Instructor, Department of Medicine, Tufts University School of Medicine; Research Fellow, William B. Schwartz Division of Nephrology, Tufts Medical Center, Boston, MA
Measurement and Estimation of Kidney Function

Edmund Huang, MD
Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD
Biological Agents in Kidney Transplantation

Alp Ikizler, MD
Department of Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN
Nutrition and Metabolism in Kidney Disease

Betrand L. Jaber, MD, MS, FASN
Associate Professor of Medicine, Department of Medicine, Tufts University School of Medicine; Vice Chair of Clinical Affairs, Department of Medicine; Director, Kidney & Dialysis Research Laboratory, St. Elizabeth's Medical Center, Boston, MA
Acute Complications Associated with Hemodialysis

Olwyn Johnston, MB, MRCPI, MD, MHSc
Clinical Assistant Professor of Medicine, Division of Nephrology, Department of Medicine; Clinical Assistant Professor of Medicine and Transplant Nephrologist, Division of Nephrology, Department of Medicine, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada
Chronic Kidney Disease and the Kidney Transplant Recipient

Rigas Kalaitzidis, MD
Postdoctoral Fellow in Hypertension, Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, IL
Hypertensive Kidney Disease

Kamyar Kalantar-Zadeh, MD, MPH, PhD
Associate Professor-in-Residence of Medicine, Pediatrics & Epidemiology Medicine, UCLA, Los Angeles, CA; Director of Dialysis Expansion & Epidemiology, Harbor-UCLA, Torrance, CA
Inflammation in Chronic Kidney Disease

Nitin Khosla, MD
Senior Fellow in Nephrology, Department of Medicine, University of California at San Diego, San Diego, CA
Hypertensive Kidney Disease

Paul L. Kimmel, MD
George Washington University, Department of Medicine, Washington, DC
Depression and Neurocognitive Function in Chronic Kidney Disease

Alan S. Kliger, MD
Clinical Professor of Medicine, Department of Internal Medicine, Yale University School of Medicine; Chief Medical Officer, Chief Quality Officer, Hospital of Saint Raphael, New Haven, CT
Frequent Hemodialysis: Physiological, Epidemiological, and Practical Aspects

Camille Nelson Kotton, MD
Clinical Director, Transplant and Immunocompromised Host, Infectious Diseases, Division of Infectious Diseases, Massachusetts General Hospital; Assistant Professor, Department of Medicine, Harvard Medical School, Boston, MA
infection in renal transplant recipients

Csaba P. Kovesdy, MD, FASN
Associate Professor of Clinical Internal Medicine, Department of Medicine, University of Virginia, Charlottesville, VA; Chief of Nephrology, Salem Veterans Affairs Medical Center, Salem, VA; Associate Professor of Medicine, Department of Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA
Inflammation in Chronic Kidney Disease

Andrew S. Levey, MD
Dr Gerald J. and Dorothy R. Friedman Professor of Medicine, Department of Medicine, Tufts University School of Medicine; Chief, William B. Schwartz Division of Nephrology, Attending Physician, William B. Schwartz Division of Nephrology, Tufts Medical Center, Boston, MA
Measurement and Estimation of Kidney Function

Adeera Levin, MD, FRCPC
University of British Columbia, St. Paul's Hospital, British Columbia Provincial Renal Agency, Vancouver, British Columbia, Canada
The Role of the Chronic Kidney Disease Clinic

John K. Leypoldt, PhD
Senior Director, Renal Division, Baxter Healthcare Corporation, McGaw Park, IL
Hemodialysis Adequacy

Philip Kam-Tao Li, MD, FRCP, FACP
Chief of Nephrology & Consultant Physician, Honorary Professor of Medicine, Department of Medicine & Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong
Peritoneal Dialysis-related Infections

Orfeas Liangos, MD, FACP, FASN
Adjunct Assistant Professor of Medicine, Department of Medicine, Tufts University School of Medicine, Boston, MA; Physician, III. Med. Klinik (Nephrology), Klinikum Coburg, Coburg, BY, Germany
Acute Complications Associated with Hemodialysis

Etienne Macedo, MD
Postdoctorate Fellow, School of Medicine, University of California San Diego, San Diego, CA
Dialytic Management for Acute Renal Failure

Colm C. Magee, MD, MPH, FRCPI
Clinical Lecturer, Royal College of Surgeons in Ireland; Consultant Nephrologist, Beaumont Hospital, Dublin, Ireland
Evaluation of Donors and Recipients

Sayeed K. Malek, MD, FACS
Clinical Director of Transplant Surgery, Brigham & Women's Hospital, Instructor in Surgery, Harvard Medical School, Boston, MA
Surgical Management of the Renal Transplant Recipient

Ravindra L. Mehta, MD
Clinical Professor, School of Medicine, University of California San Diego, San Diego, CA
Dialytic Management for Acute Renal Failure

Timothy W. Meyer, MD
Professor, Department of Medicine, Stanford University, Stanford, CA; Staff Physician, Department of Medicine, VA Palo Alto HCS, Palo Alto, CA
The Pathophysiology of Uremia

Sharon M. Moe, MD
Professor of Medicine and Anatomy and Cell Biology, Vice-Chair for Research, Department of Medicine, Indiana University School of Medicine; Staff Physician, Roudebush VAMC and Clarian Health Partners, Indianapolis, IN
Chronic Kidney Disease-mineral Bone Disorder

Nader Najafian, MD
Assistant Professor of Medicine, Renal Division, Transplantation Research Center, Brigham and Women's Hospital, Children's Hospital, Boston, Harvard Medical School, Boston, MA
Transplantation Immunobiology

Cynthia C. Nast, MD
Professor of Pathology, Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, CA
Diagnosis and Therapy of Graft Dysfunction

Akinlolu O. Ojo, MD, PhD
Professor of Medicine and Attending Transplant Nephrologist, University of Michigan Medical School, Ann Arbor, MI
Chronic Kidney Disease in Nonkidney Transplant Recipients: Hematopoetic Cell and Solid Organ Transplantation

Mark Douglas Okusa, MD
John C. Buchanan Distinguished Professor of Medicine, Department of Medicine, University of Virginia; Attending Physician, Department of Medicine, University Health of Virginia Health System, Charlottesville, VA
Pharmacological Interventions in Acute Kidney Injury

Yvonne M. O'Meara, MD, FRCPI
Senior Lecturer in Medicine, Department of Medicine, University College Dublin; Consultant Nephrologist, Department of Renal Medicine, Mater Misericordiae University Hospital, Dublin, Ireland
Recurrent and De Novo Renal Diseases After Kidney Transplantation

Priti R. Patel, MD, MPH
Medical Epidemiologist, Prevention and Response Branch, Div Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA
Hemodialysis-associated Infections

Phuong-Chi T. Pham, MD
Professor of Clinical Medicine, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles; Professor of Clinical Medicine, Department of Medicine, Nephrology Division, Olive View-UCLA Medical Center, Sylmar, CA
Diagnosis and Therapy of Graft Dysfunction

Phuong-Thu T. Pham, MD
Associate Clinical Professor of Medicine, Director of Outpatient Services, Department of Medicine, Nephrology Division, David Geffen School of Medicine at UCLA; Associate Clinical Professor of Medicine, Director of Outpatient Services, Kidney and Pancreas Transplant Program, Ronald Reagan Medical Center at UCLA, Los Angeles, CA
Diagnosis and Therapy of Graft Dysfunction

Jeffrey L. Platt, MD
Professor of Surgery and Professor of Microbiology and Immunology, Transplantation Biology; Associate Professor of Surgery and Associate Professor of Microbiology & Immunology, Transplantation Biology, University of Michigan, Ann Arbor, MI
Emerging Strategies in Kidney Transplantation

Lara B. Pupim, MD, MSCI
Department of Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN; Mitsubishi Pharma America, Inc., Warren, NJ
Nutrition and Metabolism in Kidney Disease

Emilio Ramos, MD
Clinical Professor of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD
Infection in Renal Transplant Recipients

Deborah S. Rosenthal, MA
Ferkauf Graduate, School of Psychology Yeshiva University, New York, NY
Depression and Neurocognitive Function in Chronic Kidney Disease

Maria-Eleni Roumelioti, MD
Postdoctoral Associate, Department of Medicine, Renal and Electrolyte Division, University of Pittsburgh, Pittsburgh, PA
Sleep Disorders

Venkata Sabbisetti, PhD
Research Fellow in Medicine, Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA
Acute Kidney Injury: Biomarkers from Bench to Bedside

Denise M. Sadlier, MB, PhD, FRCPI
Senior Lecturer in Medicine, Department of Medicine, University College Dublin; Consultant Nephrologist, Department of Renal Medicine, Mater Misericordiae University Hospital, Dublin, Ireland
Recurrent and De Novo Renal Diseases after Kidney Transplantation

Mark J. Sarnak, MD, MS
Professor of Medicine, Tufts University School of Medicine, Nephrologist, Tufts Medical Center, Boston, MA
Cardiovascular Disease in Patients with Chronic Kidney Disease

Tariq Shafi, MBBS, MHS
Assistant Professor of Medicine, Department of Medicine/Nephrology, Johns Hopkins University; Associate Faculty, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD
Chronic Kidney Disease: Definition, Epidemiology, Cost and Outcomes

Edward D. Siew, MD, MSCI
Clinical Instructor of Medicine, Vanderbilt University Medical Center, Department of Medicine, Division of Nephrology, Nashville, TN
Metabolic and Nutritional Complications of Acute Kidney Injury

Robert C. Stanton, MD
Principal Investigator, Chief of the Nephrology Section, Joslin Diabetes Center, Associate Professor of Medicine, Harvard Medical School, Boston, MA
Diabetic Kidney Disease: Current Challenges

Lesley A. Stevens, MD, MS
Assistant Professor of Medicine, Department of Medicine, Tufts University School of Medicine; Attending Physician, William B. Schwartz Division of Nephrology, Tufts Medical Center, Boston, MA
Measurement and Estimation of Kidney Function

Patrick J. Strollo, Jr., MD, FACCP, FAASM
Associate Professor of Medicine and Clinical and Translational Science, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA
Sleep Disorders

Terry B. Strom, MD
Professor of Medicine, Department of Medicine, Harvard Medical School; Scientific Co-Director, The Transplant Institute, Beth Israel Deaconess Medical Center, Boston, MA
Novel Diagnostics in Transplantation

Rita S. Suri, MD
Assistant Professor, Department of Nephrology, University of Western Ontario; Clinical Nephrologist, Department of Nephrology, London Health Sciences Center, London, Ontario, Canada
Frequent Hemodialysis: Physiological, Epidemiological, and Practical Aspects
Peritoneal Dialysis Prescription and Adequacy

Nicola D. Thompson, PhD
Epidemiologist, Surveillance Branch, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA
Hemodialysis-associated Infections

Stefan G. Tullius, MD, PhD, FACS
Chief, Division of Transplant Surgery, Brigham & Women's Hospital, Associate Professor of Surgery, Harvard Medical School, Boston, MA
Surgical Management of the Renal Transplant Recipient

Mark Unruh, MD, MSc
Assistant Professor of Medicine, Department of Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, PA
Sleep Disorders

Flavio Vincenti, MD
Kidney Transplant Service, University of California, San Francisco School of Medicine, San Francisco, CA
Biological Agents in Kidney Transplantation

Bradley A. Warady, MD
Professor of Pediatrics, Department of Pediatrics, University of Missouri-Kansas City School of Medicine; Interim Chairman, Department of Pediatrics, Chief, Section of Nephrology, Director, Dialysis and Transplantation, The Children's Mercy Hospital, Kansas City, MO
The Pediatric Patient with Chronic Kidney Disease

Daniel E. Weiner, MD, MS
Assistant Professor of Medicine, Tufts University School of Medicine; Nephrologist, Tufts Medical Center, Boston, MA
Cardiovascular Disease in Patients with Chronic Kidney Disease

Mark E. Williams, MD, FACP, FASN
Associate Professor of Medicine, Harvard Medical School, Co-Director of Dialysis, Beth Israel Deaconess Medical Center; Senior Staff Physician, Joslin Diabetes Center, Boston, MA
Diabetic Kidney Disease: Current Challenges

Wolfgang C. Winkelmayer, MD, ScD
Associate Professor of Medicine and Director of Clinical Research, Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA
Kidney Disease and Medications

Karl L. Womer, MD
Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD
Biological Agents in Kidney Transplantation

Jane Y. Yeun, MD
Professor of Clinical Medicine, Division of Nephrology, Department of Medicine, University of California, Davis; Staff Nephrologist, Nephrology Section, Medical Service, Veterans Administration Northern California Healthcare System, Sacramento, CA
Principles of Hemodialysis

Bessie Ann Young, MD, MPH
Associate Professor, Department of Medicine, Division of Nephrology, University of Washington; Staff Nephrologist, Primary and Specialty Care, Division of Nephrology, Veterans Affairs Puget Sound Health Care System, Seattle, WA
Timing and Initiation and Modality Options for Renal Replacement Therapy

Chapter 1

CHRONIC KIDNEY DISEASE: DEFINITION, EPIDEMIOLOGY, COST, AND OUTCOMES

Tariq Shafi, M.B.B.S., M.H.S., F.A.C.P. and
Josef Coresh, M.D., M.H.S., Ph.D.

Chronic kidney disease (CKD) is a global public health problem with a rising prevalence. Glomerular filtration rate (GFR) is considered the best overall index of kidney function, and low GFR is associated with higher risk of kidney failure requiring dialysis and cardiovascular disease, hypertension, anemia, and other metabolic complications. The last decade has seen significant improvement in recognition of the incidence, prevalence, and complications of CKD due in major part to the development of definitions of CKD by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI). The wide dissemination and adoption of K/DOQI classification, with its emphasis on routine and automated estimation of GFR from serum creatinine (eGFR), has improved recognition of CKD in many populations where it was previously under recognized, such as the elderly and women. Increased awareness of CKD and uniform classification criteria have led to a better understanding of the burden of illnesses that accompany CKD and have increased focus on developing methods to slow CKD progression and increased emphasis on early recognition and prevention of complications associated with decline in GFR. While much progress has been made, the number of therapies and clinical trials on which to base recommendations is still very limited.

DEFINITION OF CHRONIC KIDNEY DISEASE

Renal parenchymal disease is the result of a variety of acute and chronic insults that can lead to nephron loss followed by adaptive hyperfiltration in the remaining nephrons. This adaptive hyperfiltration results in long-term glomerular damage leading to proteinuria and progressive loss of renal function. The initial decline of renal function is asymptomatic, and clinical manifestations of kidney failure occur late in the course of the disease. Loss of renal function, however, is variable and can be relentless even despite optimal medical therapy. Definitions of kidney disease have therefore focused on measures of function (GFR) and measures of damage (proteinuria, anatomical abnormalities).

Prior to the K/DOQI guidelines in 2002, there were numerous definitions of CKD in use. Many of these definitions were not well understood by patients and the lay public due to the use of word "renal" and its Latin and Greek roots. Hsu and Chertow enumerated the different names used for CKD from abstracts submitted to the American Society of Nephrology meetings in 1998 and 1999 and in articles indexed in Medline.[1] They noted 23 different terms used to describe states of reduced GFR along with a number of

different and overlapping definitions of kidney failure using serum creatinine, creatinine clearance, or GFR.

The use of serum creatinine, in isolation, for defining CKD is especially problematic.[2] Mild elevations of serum creatinine can often be dismissed as clinically insignificant, and even when recognized as abnormal, the emphasis on creatinine alone may underestimate the severity of underlying kidney disease. Serum creatinine is dependent not only on creatinine clearance by the kidney but also on creatinine generation and dietary animal protein intake. Creatinine generation in turn is strongly dependent on age, gender, race, and muscle mass.[3] Many individuals including women and elderly may have decreased muscle mass and therefore lower creatinine.[4] These individuals can have moderately or severely reduced kidney function with creatinine values that may be within the distribution of "normal" population ranges. Reliance on serum creatinine alone will therefore result in a systematic underestimation of kidney disease prevalence and severity in these groups.

Considering these factors, the K/DOQI working group decided to use the word "kidney" instead of "renal" and developed an operational definition of CKD (Table 1-1).[3] CKD is defined as the presence of kidney damage for at least 3 months. Kidney damage could be either:

(1) Pathological abnormalities of the kidney such as the presence of polycystic kidney disease
(2) Presence of markers of kidney damage such as proteinuria
(3) GFR less than 60 ml/min/1.73 m^2 without any other evidence of kidney damage

The guidelines also defined a five-stage system for classification of CKD (Table 1-2). Stages 1 and 2 are defined by the presence of markers of kidney damage and distinguished from each other by the absence (stage 1) or presence (stage 2) of mildly reduced GFR. Stages 3 to 5 are based solely on the level of GFR. The staging system represents the increasing azotemic burden as GFR declines and recognizes the common manifestations of reduced kidney function such as anemia and hyperparathyroidism that can occur independent of the etiology of the underlying kidney disease (such as glomerulonephritis or hypertensive nephrosclerosis). At each stage of CKD, an action plan was proposed with the goal of improving outcomes in patients and reducing mortality based on the best, but often limited, available evidence. The K/DOQI classification system complements the traditional classification systems that are based on clinical features (such as nephrotic syndrome) or pathophysiological mechanisms (such as immunoglobulin A (IgA) nephropathy on kidney biopsy).

A major contribution of the K/DOQI guidelines is the emphasis on defining CKD based on estimated GFR (eGFR). GFR remains the best overall index of kidney function, but actual measurement of GFR is cumbersome and is reserved for special situations. K/DOQI recommended the use of equations to estimate GFR from serum creatinine using the Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) Study equation in adults and the Schwartz and Counahan-Barratt equations in children. The Cockcroft-Gault equation estimates GFR by calculating the unadjusted creatinine clearance.[5] The equation was developed in a sample of 249 men. It is used for creatinine clearance calculation in women by using a theoretical adjustment factor for lower muscle mass in women. Creatinine is actively secreted by the proximal tubule, and the secretion increases as the GFR declines. As a result, creatinine clearance overestimates the GFR, especially in the lower range of GFR in patients with advanced CKD. The Cockcroft-Gault equation also tends to underestimate the GFR in the

TABLE 1-1 Definition of Chronic Kidney Disease

CRITERIA
1. Kidney damage for $\geq$ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities • Markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests
2. GFR < 60 ml/min/1.73 m^2 for $\geq$ 3 months, with or without kidney damage

GFR, glomerular filtration rate.
Adapted from National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, Am. J. Kidney Dis. 39 (2 Suppl 1) (2002) S1-S266.

TABLE 1-2 Chronic Kidney Disease Stages: K/DOQI Classification and Updates

K/DOQI CLASSIFICATION			UPDATES			
STAGE	***DESCRIPTION***	***GFR***	***KDIGO***	***CARI***	***NICE***	
1	Kidney damage with normal or increased GFR	$\geq$ 90			"P" if proteinuria Identify rate of progression.	
2	Kidney damage with mild decrease in GFR	60-89				
3	Moderate decrease in GFR	30-59	"T" if kidney transplant	"D" if on dialysis	"P" if proteinuria	3a (eGFR 45-59)
						3b (eGFR 30-44)
4	Severe decrease in GFR	15-29				
5	Kidney failure	<15				

CARI, Caring for Australians with Renal Impairment; GFR, glomerular filtration rate in ml/min/1.73 m^2; K/DOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Health Service–National Institute for Health and Clinical Excellence.

elderly and overestimate it in edematous or obese patients. Finally, the calibration of serum creatinine for the equation is uncertain, and standardization for body surface area requires a separate step. The MDRD Study equation was developed in a sample of 1,628 patients with CKD that were screened for enrollment in the MDRD Study.[6] The equation estimates GFR adjusted to body surface area and accounts for creatinine generation by adjusting for age, gender, and race. Although the calculation of estimated GFR by the MDRD equation is mathematically complex, it has been greatly simplified by the nearly universal availability of various "calculators" in healthcare settings and by the K/DOQI initiative to have eGFR reported by the laboratory measuring serum creatinine. The MDRD equation has been widely used and independently validated in several populations, including transplant recipients.[7,8] The MDRD equation, however, underestimates GFR at higher levels of GFR. The equation has recently been updated by a new equation developed by the Chronic Kidney Disease Epidemiology Collaboration, a National Institutes of Health (NIH) sponsored initiative. This new equation, the CKD-EPI creatinine equation, was derived using pooled data from 26 studies where GFR measurement was performed.[9] Ten studies including 8254 patients served as the development dataset for the equation and 16 studies with 3896 people as the validation dataset. This new equation is at least as accurate as the MDRD equation in predicting measured GFR in patients with eGFR less than 60 ml/min/1.73 m^2, but is substantially more accurate than the MDRD study equation in individuals with eGFR above 60 ml/min/1.73 m^2. The median difference (interquartile range) between measured GFR and eGFR (bias) in the group with eGFR greater than or equal to 60 ml/min/1.73 m^2 was 3.5 (2.6, 4.5) ml/min/1.73 m^2 using the CKD-EPI equation compared with 10.6 (9.8, 11.3) ml/min/1.73 m^2 using the MDRD equation. The equation also has improved accuracy at the higher GFR level. In the group with estimated eGFR greater than or equal to 60 ml/min/1.73 m^2, using the CKD-EPI equation, 88.3% (95% Confidence Interval [CI], 86.9-89.7) of the GFR estimates were within 30% of the measured GFR (P_{30}) compared with 84.7% (95% CI, 83.0-86.3) for the MDRD equation. The equation was developed on a population that included a larger number of African Americans and older individuals compared to the MDRD equation. The CKD-EPI 2009 creatinine equation is most easily expressed separately for each gender, race, and creatinine group. This improved equation will enhance clinical decision making in individuals with CKD stages 1 to 3 and will reduce misclassification while improving prevalence estimates of the disease burden of CKD.

The K/DOQI classification system for CKD has been endorsed by many international societies and groups including:

- **Kidney Disease: Improving Global Outcomes (KDIGO).** KDIGO accepted the K/DOQI guidelines with the following additional recommendations:[10]
  - Infer chronicity based on documentation of kidney disease for 3 months or longer.
  - Consider all patients with kidney transplant to have CKD and indicate that by "T".
  - Designate "D" for CKD stage 5 patients on peritoneal dialysis or hemodialysis.
  - Consider threshold for microalbuminuria as greater than 30 mg of albumin per gram of creatinine (greater than 30 mg/g)
- **The Canadian Society of Nephrology (CSN)** endorsed the K/DOQI classification system with the modifications proposed by KDIGO.[11]
- **The Caring For Australians with Renal Impairment (CARI) Guidelines—Australia/New Zealand:** The CARI guidelines also endorsed the K/DOQI guidelines with KDIGO modifications and recommended addition of suffix "P" for proteinuria.[12]
- **The National Health Service—National Institute for Health and Clinical Excellence (NICE) Chronic Kidney Disease Guidelines.**[13] The United Kingdom guidelines for CKD also endorsed the K/DOQI classification. The guidelines recommend:
  - Subdividing stage 3 CKD into 3a (eGFR 45 to 59 ml/min/1.73 m^2) and 3b (eGFR 30 to 44 ml/min/1.73 m^2)
  - Use of suffix "P" for proteinuria (greater than 0.5 g/24 hours or protein:creatinine ratio greater than or equal to 50 mg/mmol) or albuminuria (greater than or equal to 30 mg/mmol)
  - Identifying progressive disease (eGFR decline greater than 5 ml/min/1.73 m^2 in 1 year or greater than 10 ml/min/1.73 m^2 within 5 years)

It is noteworthy that all guidelines suggest that only a subset of CKD patients be referred.The K/DOQI hypertension guidelines suggest referral to a nephrologist for CKD patients with advance disease (stages 4 and 5) proteinuria (adding microalbuminuria and retinopathy in diabetic patients), rapid progression of CKD, or uncontrolled complications (hyperkalemia and resistant hypertension). These criteria suggest only 19% of U.S. patients with stage 3 CKD should be referred to a nephrologist.[14] Thus, the current definition of CKD addresses the full spectrum of disease, including milder cases that do not require specialty care. This shift in emphasis suggests a partnership with general practitioners in caring for the full spectrum of disease.

Strengths and Limitations of the Current Chronic Kidney Disease Classification System

Strengths

The K/DOQI classification system for CKD has led to reporting of eGFR with serum creatinine. Reporting of eGFR is important and "the only reason to measure serum creatinine is to assess GFR."[15] Determination of the severity of kidney disease with serum creatinine is difficult due to the log-linear relationship between serum creatinine levels and measured GFR and multiple non-GFR determinants of serum creatinine concentration. Less than 50% of individuals with eGFR below 30 ml/min/1.73 m^2, the group with the highest risk of progression to end-stage renal disease (ESRD), recall ever being told about weak or failing kidneys.[16] Even physicians fail to recognize the presence of CKD with low levels of eGFR when relying on serum creatinine measurement alone.[17] As discussed in the next section, over 100,000 persons reach ESRD every year and require renal replacement therapy. Therefore, early diagnosis is important to prevent progression and to prepare for

renal replacement therapy. Early detection of CKD, by automated reporting of eGFR, may allow early referral of the highest risk subset of CKD patients to nephrologists. Early referral is associated with improved survival with and without dialysis and with reduction in the number of hospitalizations.[18–21] There is widespread agreement that CKD classification has raised awareness of the full spectrum of CKD and its wide range of complications. The challenge and controversy is that increased awareness also points a brighter spotlight on gaps in the knowledge base, particularly with regard to efficacy, cost effectiveness, and thresholds for interventions. Changing the practice from excluding severe CKD patients from trials to including CKD patients and focusing on testing efficacy in this high risk population may be one of the most important outcomes of a clear and simple classification system centered on uniform reporting of the key markers of kidney damage (albuminuria) and function (eGFR).

Limitations

The current classification system also has its limitations, and these have been actively debated.[22–25] There is inherent error and variability in the measurement of GFR, and there are limitations in the accuracy and precision of the estimating equations used to predict GFR. As discussed previously, the MDRD equation performs best at GFR levels below 60 ml/min/1.73 m^2. The creatinine estimating equations suffer the limitations imposed by serum creatinine as an endogenous marker of GFR and are not reliable at extremes of body weight or when a patient's creatinine metabolism is not in steady state such as in acute kidney injury. Therefore, there has been criticism of estimating GFR using the MDRD Study equation in general population samples, defining CKD based on a single eGFR cutoff rather than age specific cutoff, and defining CKD stages 1 and 2 based on persistent microalbuminuria without significant proteinuria as having a "disease."[23] Application of the CKD definitions to the population provides a useful indicator of the implications of the definition. However, it also clearly points out the large number of individuals meeting the CKD definition, particularly among many older individuals who will never progress to ESRD. Some fear that these individuals may undergo unnecessary diagnostic testing[23] while others suggest the potential benefit of alerting physicians to optimize existing therapies and avoid nephrotoxic medications.[22] General screening for CKD using eGFR is unlikely to be cost-effective. The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) uses a targeted screening protocol based on the presence of hypertension, diabetes, cardiovascular disease, and first-degree relatives with ESRD.[26,27] Finally, the presence of CKD has been misinterpreted as indicating a need for referral to a nephrologist despite guidelines suggesting that only a subset of patients require specialty care. The 2002 K/DOQI guidelines recommend nephrology referral for patients with eGFR less than 30 ml/min/1.73 m^2, and a similar threshold for referral was endorsed by the CARI guidelines.[3,12] The NICE guidelines also recommend nephrology referral for patients with eGFR less than 30 ml/min/1.73 m^2 with added emphasis on patients with significant proteinuria and those with rapid declining GFR.[13]

Future Directions

The concept of classifying CKD based on eGFR has greatly improved our understanding of the epidemiology of CKD. The focus is now shifting toward risk stratification and identification of the individuals at the highest risk of progression that may benefit from early referral and evaluation. Another challenge is to recognize the full range of preventable complications of CKD. The early focus was on cardiovascular disease and mortality as the most common cause of death and kidney failure as the end-stage kidney outcome. However, a wide-spectrum acute kidney injury is likely more common in the presence of underlying CKD, as are suboptimal medical care, including inappropriate medication dosing, and nonkidney outcomes such as infection and pneumonia. In this context, a KDIGO Controversies Conference on "Chronic Kidney Disease: Definition, Classification and Prognosis" was held in October 2009. The conference gathered data and focused on prognosis of CKD as well as discussed revision to the present CKD stages. Some of these results have been recently published and quantitatively demonstrate that eGFR <60 ml/min/1.73 m^2 is an independent predictor of mortality in the general population.[28]

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

In this section, we will discuss the distribution and determinants of the occurrence of CKD. We will review the available epidemiological evidence of some of the common causes of CKD. We define "incidence" as the occurrence or diagnosis of CKD in an individual who was disease-free at an earlier time. We define "prevalence" as the distribution of the individuals with CKD in the population at any given time. Incidence refers to occurrence of new disease, whereas prevalence is a "snapshot" of disease distribution in a population at a particular time. Incidence of a disease is dependent on the presence of a susceptible population with etiological factors for development of disease whereas prevalence depends on the incidence of the disease, and duration of the disease. Incidence of CKD, for example, depends on the population distribution of diabetes, hypertension, and other etiological risk factors for CKD. Prevalence of CKD will depend on the incidence of CKD and the life span of individuals and outcomes of other causes of illness and death, with atherosclerotic cardiovascular heart disease being the leading cause of death in CKD. Increasing population burden of obesity, diabetes, and hypertension will increase incidence. Improved treatment of cardiovascular heart disease is likely to prolong the life span and lead to increase in prevalence of CKD.

Most epidemiological descriptions of CKD (for patients not on dialysis) are limited to prevalence estimates because documentation of occurrence of CKD requires establishing an earlier disease-free state followed by a long period of observation with repeated assessment of kidney function. More data are available on the incidence and prevalence of kidney failure treated with renal replacement therapy due to availability of registries in most developed countries. The United States Renal Data System (USRDS) provides comprehensive description of CKD and ESRD incidence and prevalence. In addition, the system has expanded to cover treatment and

outcomes in the administrative data and more recently has included detailed information on CKD.[29] The Centers for Disease Control (CDC) has also developed a project to provide surveillance for CKD using a wide range of parameters and data sources that will be tracked continuously.[30]

Etiology of Chronic Kidney Disease

CKD can result from any underlying kidney disease that results from either acute kidney injury or a slowly progressive kidney disease. Discussion of all the causes of kidney disease is beyond the scope of this chapter. Instead, we will focus on available epidemiological data of a few common causes of CKD. From an epidemiological perspective, it is important to recognize that etiologies of CKD, as determined by ESRD registries, are limited by a number of factors. ESRD patients are disease "survivors" who initiate renal replacement therapy (dialysis and kidney transplantation) and thus reflect the progressive forms of CKD. Initiation of renal replacement therapies is also determined by physician practice characteristics, availability of resources, and societal and cultural norms. Finally, registry data are dependent on completion of regulatory forms that may or may not be accurate.

The importance of established risk factors for ESRD was recently highlighted in a report of 177,570 Kaiser Permanente of Northern California members who participated in the Multiphasic Health Testing Services Program in Oakland and San Francisco between June 1, 1964 and August 31, 1973.[31] Initiation of ESRD treatment was ascertained via linking with the USRDS database and identifying 842 cases of ESRD. Higher risk of ESRD was seen with male gender, older age, proteinuria, diabetes mellitus, lower educational attainment, African American race, higher blood pressure, body mass index, and serum creatinine level. These data are in agreement with the USRDS 2008 Annual Data Report (ADR) demonstrating diabetes and hypertension as the leading primary reported diagnoses for ESRD (Figure 1-1) with the highest rates of ESRD in African Americans and Native Americans as well as seminal reports from the Multiple Risk Factor Intervention Trial screenees and population based case-control studies.[32–34]

Diabetes

Diabetes is the leading cause of CKD and ESRD worldwide. There has been a global increase in prevalence of diabetes over the last 2 decades, raising concerns about a rise in CKD prevalence to follow. Diabetic nephropathy occurs in both type I and type II diabetes.

Type I Diabetes The incidence of type I diabetes has progressively increased.[35] The clear cut clinical onset of type I diabetes allows better estimation of the time to development of diabetic nephropathy compared to type II diabetes. Most studies reporting the incidence of diabetic nephropathy rely on urine albumin excretion as a surrogate marker for the presence of diabetic nephropathy. It is, however, important to note that morphological changes of diabetic glomerulosclerosis precede the occurrence of albuminuria, although albuminuria itself is a risk factor for progression of diabetic nephropathy.[36]

The occurrence of diabetic nephropathy in type I diabetes has changed with focus on improved glycemic and blood pressure control. Prior to the modern day intensive treatment strategies, diabetic nephropathy, as detected by microalbuminuria, was described in 20% to 30% of the patients after 15 years of follow-up, and ESRD was described in 4% to 17% of the patients at 20 years.[37,38,39] More recently, a study from Sweden noted a much lower incidence of diabetic nephropathy (8.9% at 25 years), and another from Finland reported a much lower incidence of ESRD (2.2% at 20 years), which may reflect the protective effects of intensive blood pressure and glucose control.[40,41]

Type II Diabetes Sedentary lifestyle and obesity are contributing to a rising prevalence of type II diabetes.[42] Recent data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 demonstrated that among adults aged 20 to 39 years, 28.5% were obese; among those 40 to 59 years, 36.8% were obese; and among those aged 60 years or older, 31% were obese.[43] Obesity was defined as a body mass index of 30 kg/m^2 or higher. The prevalence of diabetes was 2.4% among normal weight individuals but rose to 14.2% among those with body mass index of 40 kg/m^2 or higher.[44]

In the United States, age, gender, and race adjusted incidence rates of ESRD attributed to diabetes has doubled in the last decade.[32] In the United Kingdom Prospective Diabetes Study, among 5097 patients with type II diabetes enrolled in the study, at 10 years, the prevalence of microalbuminuria was 24.9%, macroalbuminuria was 5.3%, and serum creatinine greater than 2 mg/dl or the need for renal replacement therapy was 0.8%.[45] The progression to microalbuminuria was 2% per year, from microalbuminuria to macroalbuminuria was 2.8% per year, and from macroalbuminuria to serum creatinine greater than 2 mg/dl or renal replacement therapy was 2.3% per year.

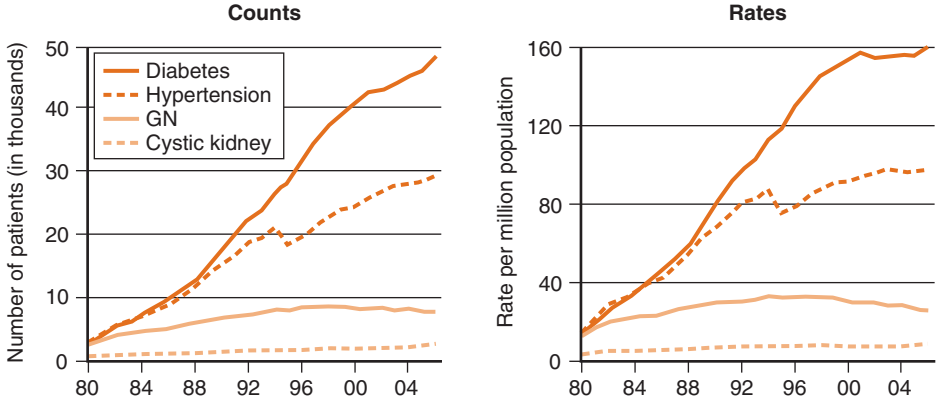


FIGURE 1-1 Adjusted U.S. Incidence of ESRD by Primary Diagnosis. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 1: Fig 2.8. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

Hypertension

Hypertension is the second most commonly reported etiology of ESRD in the United States.[32] The overall prevalence of hypertension in the United States determined using the NHANES data is 29.3%.[46] The prevalence rates of hypertension in the United States have remained stable between 1999 to 2000 and 2003 to 2004. High prevalence rates have also been described in other populations. In the 2002 China National Nutrition and Health Survey, about 153 million or one in six Chinese adults were hypertensive. Similar to diabetes, the rising prevalence of hypertension also reflects the increasing obesity in the population.

Hypertension precedes the development of ESRD with progressively higher risk at higher blood pressure.[33,47–49] In 1091 participants of the African American Study of Kidney Disease, with optimal blood pressure control and use of angiotensin-converting enzyme inhibitors, the 10-year cumulative incidence of doubling of serum creatinine, ESRD, or death was 53.9%. The study showed that excellent control of hypertension among African Americans with CKD is possible and that in this setting, average loss of kidney function was still approximately 2 ml/min/1.73 m^2 per year, but one third of participants showed slow to no decline in GFR (< 1ml/min/1.73 m^2 per year).[50] However, randomization to low blood pressure versus conventional (mean arterial pressure less than 92 mm Hg vs. 102–107 mm Hg) did not show the expected benefit. This suggests there is more to learn about optimizing therapy and the difficulties of studying progression when the control group does not have proteinuria and achieves conventional blood pressure targets. Hypertension is also associated with rapid progression to ESRD in patients with other forms of kidney disease. Finally, recent genetic studies implicate the myosin heavy chain 9 (MYH9) genetic variation as a major contributor to the excess risk of nondiabetic ESRD among African Americans and indicate a shared etiology with focal segmental glomerulosclerosis.[33,47,49,51,52]

Glomerulonephritis

Glomerulonephritis is the third most common cause of ESRD.[32] The diagnosis of glomerulonephritis requires a kidney biopsy. Advances in percutaneous kidney biopsy techniques are probably responsible for an increasing diagnosis of glomerulonephritis rather than a rising incidence rate. There remains a large variation in the biopsy practices of nephrologists worldwide; patients with isolated hematuria are more likely to undergo kidney biopsy in Asia than in the United States or Europe.[53]

IgA nephropathy is the most common glomerulonephritis in the world, especially among Caucasians and Asians. It is relatively rare in blacks. In a report of 13,519 kidney biopsies performed from 1979 to 2002 in China, IgA nephropathy accounted for 45% of the primary glomerulonephritis.[54] Idiopathic focal segmental glomerulosclerosis is the most common cause of ESRD caused by primary glomerular disease in the United States.[55] Analysis of the USRDS data suggests that the proportion of ESRD attributed to focal segmental glomerulosclerosis in the non-HIV population has increased elevenfold; from 0.2% in 1980 to 2.3% in 2000 with a fourfold higher risk in African Americans compared to Caucasians and Asians. Whether this risk represents a true increase in the incidence of focal segmental glomerulosclerosis (FSGS) or is a reflection of newer classification and biopsy practices remains to be determined, but a similar trend has also been noted in the results of kidney biopsies performed in the Unites States for diagnosis of nephrotic syndrome in adults. In a kidney biopsy series reported by Haas and colleagues, data from 1000 kidney biopsies performed between 1976 and 1979 was compared to 1000 kidney biopsies performed between 1995 and 1997.[56] During the 1976 to 1979 period, the relative frequencies of membranous (36%) and minimal-change (23%) nephropathies and of focal segmental glomerulosclerosis (15%) as causes of unexplained nephrotic syndrome were similar to those observed in previous studies during the 1970s and early 1980s. In contrast, from 1995 to 1997, focal segmental glomerulosclerosis was the most common cause of this syndrome, accounting for 35% of cases compared with 33% for membranous nephropathy. During the 1995 to 1997 period, focal segmental glomerulosclerosis accounted for more than 50% of cases of unexplained nephrotic syndrome in black adults and for 67% of such cases in black adults younger than 45 years. Although the relative frequency of nephrotic syndrome due to focal segmental glomerulosclerosis was two to three times higher in black than in white patients during both study periods, the frequency of focal segmental glomerulosclerosis increased similarly among both racial groups from the earlier to the later period.

In 2008, two groups found that a common genetic variation in the MYH9, a nonmuscle myosin found in more than one third of African Americans but less than 1% of European Americans increases the risk of focal segmental glomerulosclerosis and nondiabetic ESRD, providing a major breakthrough in our understanding of the biology of focal sclerosis in African Americans.[51,52]

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease is a common disorder occurring in approximately 1 per 800 live births. It affects 500,000 persons in the United States and is responsible for 7% to 10% of ESRD cases.[57] Autosomal dominant polycystic kidney disease can lead to ESRD in childhood, but usually progression to kidney failure occurs after the fourth decade of life. The risk of progression to ESRD is less than 2% below age 40 years, 20% to 25% by age 50, 35% to 45% by age 60, and 50% to 75% by age 70.[58]

Incidence of Chronic Kidney Disease

Incidence of CKD is difficult to ascertain as it requires establishment of a cohort with normal kidney function at baseline with serial measurements of kidney function over a long period. As a result, few studies report the incidence of CKD. Furthermore, most studies are unable to apply the requirement for chronicity (more than 3 months duration). Incidence of CKD was examined in the 2585 participants of the Framingham cohort who attended both a baseline examination in 1978 to 1982 and a follow-up examination in 1998 to 2001 and who were free of kidney disease at baseline. CKD was defined as eGFR (by MDRD equation) in the fifth or lower percentile (≤ 59.25 ml/min/1.73 m^2

in women, ≤ 64.25 ml/min/1.73 m^2 in men). CKD developed in 9.4% of participants over the follow-up period and was associated with baseline GFR, diabetes, hypertension, and smoking.[59] Incident CKD was examined in the Atherosclerosis Risk in Communities Study participants, including 3859 African American and 10,661 white adults, aged 45 to 64 years without severe kidney dysfunction at baseline in 1987 to 1989. Incident CKD was defined as hospitalization or death with kidney disease or increase in serum creatinine level of 0.4 mg/dl. During median follow-up of 14 years, CKD developed in 1060 individuals (incidence per 1000 person-years: 5.5 overall; 8.8 in African Americans and 4.4 in whites).[60] Incidence of new-onset proteinuria may also reflect incident CKD. This was assessed in a 10-year prospective cohort study of 104,523 Korean men and 52,854 women, aged 35 to 59 years, who attended Korea Medical Insurance Corporation health examinations and who did not have proteinuria at baseline. Incident proteinuria developed in 3951 men (3.8%) and 1527 women (2.9%), and the associated risk factors were diabetes, male gender, and obesity.[61]

There is no accepted definition of CKD incidence. A recent comparison of different definitions included several alternatives. Incidence among 14,873 middle-age adults with eGFR greater than 60 ml/min/1.73 m^2 at baseline was defined as: (1) low eGFR (< 60 ml/min/1.73 m^2), (2) low and declining (≥ 25%) eGFR, (3) increase in serum creatinine (≥ 0.4 mg/dl) at 3 or 9 year follow-ups, and (4) CKD-related hospitalization or death. These definitions identified progressively fewer cases (1086, 677, 457, and 163 cases, respectively). There was relatively good agreement among definitions 1 to 3, but definition 4 identified mostly different cases. Risk factor associations were consistent across definitions for hypertension and lipids. Diabetes showed a stronger association with hospitalization, and gender differed in direction and magnitude across definitions.[62]

A complementary approach to incidence is to examine the rate of decline in eGFR. This is particularly effective in high risk populations but has been applied to general population studies as well.[63,64]

Prevalence of Chronic Kidney Disease

Prevalence of CKD can be inferred from registries of patients with advanced kidney failure requiring dialysis. Not all patients, however, progress to ESRD. Many patients experience a slow decline in GFR and can avoid dialysis for a long period. Many others will succumb to complications of CKD and cardiovascular disease without ever starting dialysis. In a study of 220 consecutive patients at a Veterans Administration Medical Center renal clinic who met the definition of CKD (eGFR < 60 ml/min/1.73 m^2 or urine protein/creatinine ratio of > 0.22 g/g), the cumulative incidence of mortality over 7 years was 18.5%, and that for ESRD was 17.6%.[65] Prevalence estimates in ESRD registries reflect not only incidence and survival but also acceptance criteria into the dialysis programs, which vary over time and place. In the next two sections, we will first present information on the prevalence of CKD not on dialysis followed by the prevalence of ESRD.

Prevalence of Chronic Kidney Disease (Not on Dialysis)

The most rigorous prevalence estimates for CKD in the United States are based on the analysis of the NHANES. The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the U.S. civilian noninstitutionalized population conducted by the National Center of Health Statistics, which is a branch of the CDC. The NHANES were conducted from 1988 to 1994 in two phases (from 1988 to 1991 and from 1991 to 1994) and starting from 1999 to 2000 in 2-year phases. Prevalence estimates from NHANES are based on participants that were older than 20 years and did not have a missing serum creatinine concentration. Serum creatinine in NHANES was measured using the kinetic rate Jaffe method, and the creatinine values were calibrated to the Cleveland Clinic Research Laboratory. Albuminuria was assessed using a spot urine sample and calculation of urine albumin-to-creatinine ratios. Estimates of persistence of albuminuria were based on a sample of 1241 patients in NHANES from 1988 to 1994 that underwent repeat measurements. The number of people with albuminuria is limited and contributes to imprecision, but trends over time assume constant persistence based on these data. The CKD stages are based on the K/DOQI classification system.

The prevalence estimates for the U.S. population have recently been revised using the CKD-EPI creatinine equation.[9] The study population for these estimates included 16,032 participants that were older than 20 years, completed examination in the mobile center, were not pregnant or menstruating, and were not missing serum creatinine measurements. GFR was not measured in NHANES, but is estimated using serum standardized serum creatinine measurements. Estimated GFR was calculated using the CKD-EPI creatinine MDRD Study equations. Individuals with eGFR less than 15 ml/min/1.73 m^2 were excluded and those with eGFR greater than 200 ml/min/1.73 m^2 were truncated at that level. The mean GFR (standard error) in the U.S. population using the CKD-EPI equation was 93.2 (0.39) ml/min/1.73 m^2 compared with 86.3 (0.40) ml/min/1.73 m^2 for the MDRD equation. The revised equation results in a shift to the right in GFR values at estimated GFR greater than or equal to 45 ml/min/1.73 m^2; below that level the GFR distribution remains unchanged (Figure 1-2). The overall prevalence of CKD in adults in the United States is 11.5% (95% CI, 10.6 to 12.4), which translates to 23.2 (95% CI, 21.3 to 25.0) million people in the United States with CKD (Table 1-3). This estimate is lower than the estimated 13.1% based on the MDRD Study equation. The prevalence of CKD stages 1 through 4 based on NHANES 1996 to 2006 are: 2.24% (stage 1), 2.56% (stage 2), 6.32% (stage 3), and 0.4% (stage 4). Compared to the prevalence estimates based on MDRD equation, the CKD-EPI equation eGFR leads to a lower prevalence of CKD estimates in women (compared to men) and in whites (compared to blacks). As a result, the prevalence of CKD stages 3 and 4 are not statistically higher in women versus men and in whites versus blacks as was the case using prevalence estimates based on MDRD Study eGFR. Using the CKD-EPI equation, the prevalence estimates of CKD for those older than 70 years are similar to the MDRD equation.

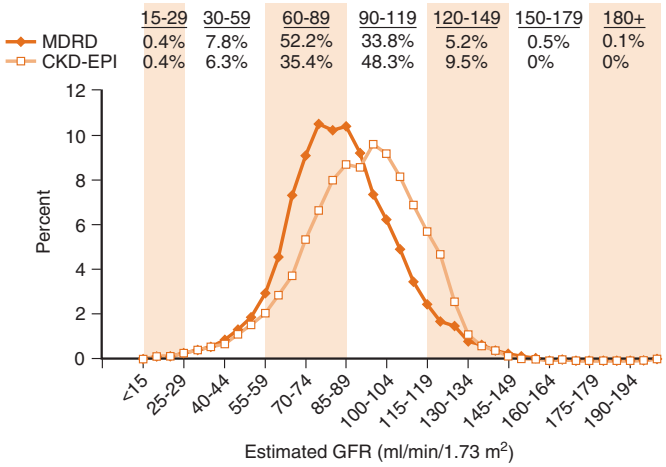


FIGURE 1-2 Comparison of distribution of estimated glomerular filtration rate (GFR) and chronic kidney disease (CKD) prevalence by age in the United States. (NHANES 1999-2004). (Adapted from A.S. Levey, L.A. Stevens, C.H. Schmid, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150[9] [2009] 604-612.)

CKD prevalence information in the United States is also available through claims data for services provided to healthcare beneficiaries. Lack of a universal healthcare system in the United States limits the ability to obtain these data. Although prevalence estimates from populations based samples, such as NHANES, are more standardized and representative for estimating disease prevalence, review of claims-based data allows for an estimation of provider assessment of CKD, estimation of costs associated with CKD care, and a larger sample size. The 2008 USRDS ADR provides prevalence estimates of CKD based on claims data from Medicare (65 years and older), Ingenix i3 dataset, and Thomson Healthcare MarketScan Data. The Ingenix i3 database is a commercial and noncapitated health plan database covering employees from multiple employers within a single insurer. It includes claims data and laboratory-based data, allowing linking of CKD claims with lab-based definitions of CKD. The Thomson Healthcare MarketScan Data includes specific health services records for employees and their dependents in a selection of large employers, health plans, and government and public organizations. The Thomson database includes health claims data for about 10.5 million people but does not include laboratory data. Figure 1-3 shows the distribution of claims data using these three databases. CKD claims are much more frequent in the Medicare population. There also appears to be a marked discrepancy between CKD defined by lab data in Ingenix i3 and claims for CKD; only 0.13% of subjects have claims for CKD stages 3 to 5 compared to 10.5% based on laboratory estimates. These data indicate that CKD remains largely unrecognized, and consequently, metabolic complications of CKD are unlikely to be identified and treated.

The widespread acceptance of the K/DOQI classification system has allowed estimation of CKD prevalence using eGFR. Table 1-4 presents a summary of literature on CKD prevalence reported in large population samples. The

TABLE 1-3 Prevalence of Chronic Kidney Disease in the US based on NHANES 1996-2006 and the CKD-EPI 2009 Creatinine Equation for Estimating GFR

STAGE	DESCRIPTION	eGFR	PREVALENCE % (95% CI)	N (1000s) (95% CI)
Stages (1-5)			11.52 (10.62-12.43)	26,247 (24,264-28,223)
1	Kidney damage with normal or increased GFR	≥ 90	2.24 (1.74-2.77)	3412 (2624-4255)
2	Kidney damage with mild decrease in GFR	60-89	2.56 (2.05-3.07)	6443 (5212-7650)
3	Moderate decrease in GFR	30-59	6.32 (5.79-6.86)	15687 (14,364-16,992)
4	Severe decrease in GFR	15-29	0.4 (0.29-0.5)	705 (519-892)
5	Kidney failure	≤ 15	NA	NA

eGFR, estimated glomerular filtration rate in ml/min/1.73 m²; NHANES, National Health and Nutrition Examination Surveys.

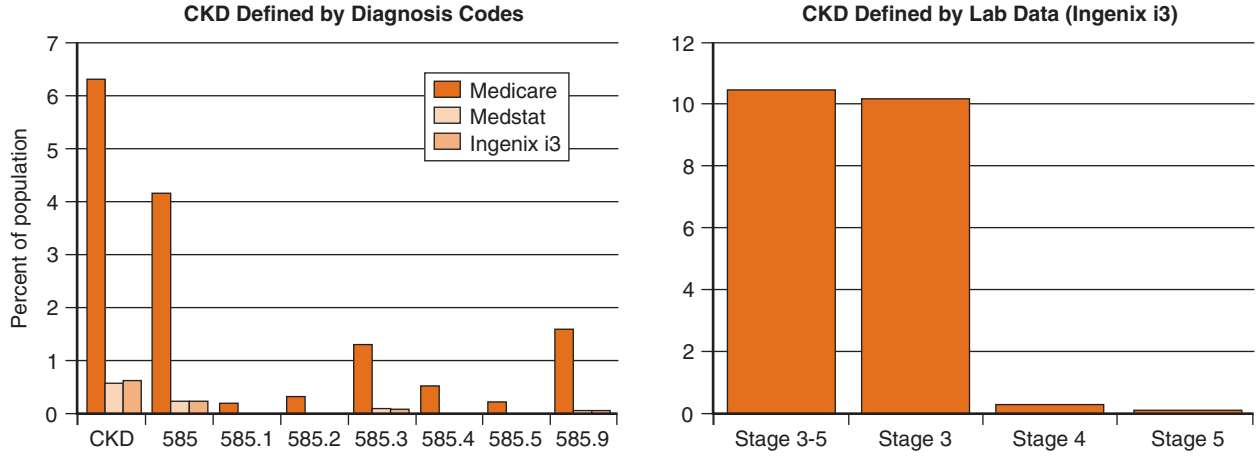


FIGURE 1-3 Chronic kidney disease (CKD) prevalence in the United States by CKD stage and dataset. (Data from U.S. Renal Data System, USRDS 2008 Annual Data report: volume 1: Fig 2.7. atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

TABLE 1-4 Prevalence Studies of Chronic Kidney Disease

STUDY	SOURCE POPULATION	COUNTRY OR REGION (AGE, YR)	N	PROTEINURIA/ ALBUMINURIA (CUTOFF) (%)	HEMATURIA (%)	GFR ≤ 60 ml/min/ 1.73 m²	
						OVERALL (%)	*AGE DEPEND-ENCE (%)*
NHANES[9]	GP (PS)	U.S. 1999-2006 (20+)	16,032	9.3 (>30 mg/g) Persistent albuminuria estimate - 6.8 (4.8 with eGFR>60)	NA	CKD-EPI 6.7[C] MDRD 8.2[C]	CKD-EPI 0.18-37.8 MDRD 0.55-37.4
REGARDS[125]	GP (PS)	Southeastern U.S. (45+)	20,667	NA	NA	43.3[C]	19.3-71
Kaiser[82]	Clinical	U.S. Northern California (20+)	1120	NA	NA	17.5[C]	Strong
KEEP[126]	High-risk	U.S.	11,246	32.5	3	14.9	Strong
NEOERICA[127]	Clinical	U.K. region (0-90+)	28,862	NA	NA	4.9	0.2-33.4
Salford[128]	Diabetes	U.K., Salford region (adult)	7596	9	NA	27.5	Strong
SAPALDIA[129]	GP (PS)	Swiss 1991 (adult)	6317	NA	NA	NA	0-35
HUNT II[130]	GP (Cohort)	Norway, Nord-Trøndelag 1995-1997 (20+)	65,181	5.9 (>30 mg/g)	NA	4.4[C]	0.2-18.6
Ausdiab[131]	GP (PS)	Australia (25+)	11,247	2.4 (>200 mg/g)	4.6	11.2	0-54.8
Aboriginies[132]	High-risk (V)	Australia, Tiwi (18+)	237	44	-	12	Strong
InterAsia[133]	GP (PS)	China (35-74)	15,540	NA	NA	2.5[C]	0.7-8.1
Beijing[134]	GP (V)	China, Beijing (40+)	2310	8.4 (S)	0.7	4.9[C]	0.3-11.5
Okinawa[135]	GP (V)	Japan, Okinawa (30-79)	6980	NA	NA	NA	NA
Okinawa Screening[95]	GP (V)	Japan, Okinawa GHMA (20+)	95,255	47.4 (≥1=)	NA	42.6	Strong
Karachi[136]	GP (V)	Pakistan, Karachi (40+)	1166	NA	NA	10	6-21.2
Thailand EGA[137]	Workplace	Thailand, Nonthaburi 1985 (35-55)	3499	2.64 (1+)	NA	1.7	Strong
Saarland[138]	GP	Germany, Saarland 2002 (50+)	9806	11.9% (>20 mg/L)	NA	17.4%	13.2-23.9
TLGS[139]	PS	Tehran, Iran 2000 (20+)	10,063	NA	NA	18.9	1.8-76.6
Polnef[140]	PS	Starogard Gdanski, Poland (18+)	2471	15.6 % (≥ 1+)	NA	8.8	Strong
PDMRA[141]	PS	Kinshasa, Democratic Republic of Congo (20+)	503	5% (>300 mg/d)	NA	8.0	Strong
Gubbio[142]	PS	Gubbio, Italy (18+)	4574	NA	NA	6.4%	0.4-31.6
Reykjavik Heart Study[143]	CS	Reykjavik, Iceland 1996 (34+)	19,381	NA	NA	7.2%	Strong

[C]Some calibration of serum creatinine to the MDRD research laboratory.
Age dependence shows the prevalence from the youngest to the oldest age group studied.
Source population: cohort, existing clinical or workplace population without specific criteria noted; GP, general population; PS, probability sample; V, volunteer sample.

populations for these estimates are varied, and some include probability sampling (allowing for generalization to a larger population), screening of high-risk population groups, or cohorts of people in clinics or in workplace. The surveys using probability sampling methods, such as the NHANES, the InterAsia Study, and AusDiab offer many advantages over the other sampling designs. Volunteer populations inherently suffer from selection biases that are reduced, though not eliminated, using probability sampling. Use of probability samples also allows generation of population estimates using appropriately applied weights. The disadvantages of cross-sectional estimates include the selection of diseases with a slow onset and prolonged duration as those with the most rapidly progressing disease may be too sick or die prior to be included in the survey. Prevalence estimates in the reported studies are quite varied reflecting the nature of the study population. Presence of albuminuria or proteinuria as a marker of kidney damage is in the range of 5% to 10% in these varied populations.

Incidence of End-Stage Renal Disease

Patients with advanced CKD, typically stage 5 (eGFR less than 15 ml/min/1.73 m^2), that start renal replacement therapy are referred to as having reached ESRD. Renal replacement therapy includes hemodialysis, peritoneal dialysis, and kidney transplantation. It is important to recognize

that kidney transplantation can be performed once the eGFR is less than 20 ml/min/1.73 m^2 and before dialysis is started if there is an available kidney donor or a matched deceased donor kidney becomes available (preemptive transplantation). The use of the term ESRD in the United States dates back to 1972 when the U.S. Congress passed legislation authorizing the End Stage Renal Disease (ESRD) program under Medicare (section 299I of Public Law 92-603). Coverage for ESRD, considered a "rare" disease at the time, was authorized for all individuals regardless of their age if they would otherwise be eligible for social security benefits. In the United States, the USRDS collects, analyzes, and distributes information about ESRD. The USRDS is funded by the National Institute of Diabetes and Digestive and Kidney Diseases in conjunction with the Centers for Medicare & Medicaid Services. The USRDS has become an excellent resource for providing precise data on ESRD and publishes an ADR summarizing its findings. The 2008 ADR includes data up until 2006 with projections up to the year 2020. The most up-to-date data are available at www.usrds.org, and for the overall incidence and prevalence data, the 2-year lag period may be reduced in the future.

In 2006, 110,854 persons reached ESRD reflecting an age, race, and gender adjusted incidence of 360 per million population (Figure 1-4). Growth in the incident counts was 3.4% and for the incidence rate was 2.1% over the 2005 rate. This represents an increase in incidence after 4 years where the yearly incidence rates were less than 1%. The incidence rates of ESRD have changed substantially since the program's inception. From 1980, the incidence rate increased by 155% to 1990 (217 per million population) and 295% by 2000 (337.5 per million population). Similar trends were noted in a cohort of 320,252 members of the Kaiser Permanente Cohort in Northern California where the likelihood of ESRD increased by 8% per year from 1973 to 2000.[66]

Several factors play a role in the rising incidence of ESRD, but perhaps the most important reason is liberal criteria for accepting patients for renal replacement therapy.[32] With aging and increased population burden of diabetes, hypertension, and obesity, the absolute numbers of patients initiating renal replacement therapy continues to increase. The median age of incident ESRD patients was 64.4 years in 2006. Adjusted for age, sex, and race, the incidence of ESRD has largely stabilized for all but the oldest age groups. For those older than 75 years, ESRD incidence increased by 11% to 1744 per million population (Figure 1-5). Between 1996 and 2003, the rates of dialysis initiation among octogenarians and nonagenarians increased by 57%.[67] Rising prevalence of CKD is also a possible contributing factor to increasing incidence of ESRD. The number of patients with diabetes listed as the primary cause of ESRD continues to increase. In addition, diabetes is associated with a higher rate of ESRD ascribed to other causes.[29] In 2006, 48,157 persons (159 per million population) with incident ESRD were diabetic, representing a 4.6% increase compared to 2005 and a 17.2% increase compared to 2000. In contrast, the incidence

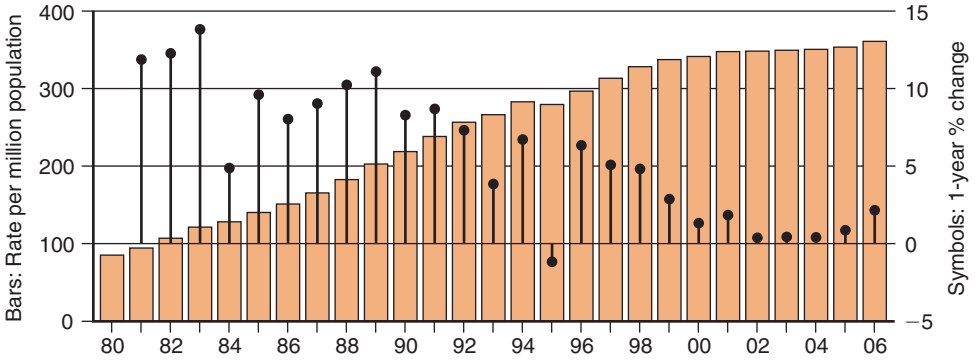


FIGURE 1-4 Adjusted U.S. incidence rates of ESRD and annual percent change. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 2.3. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

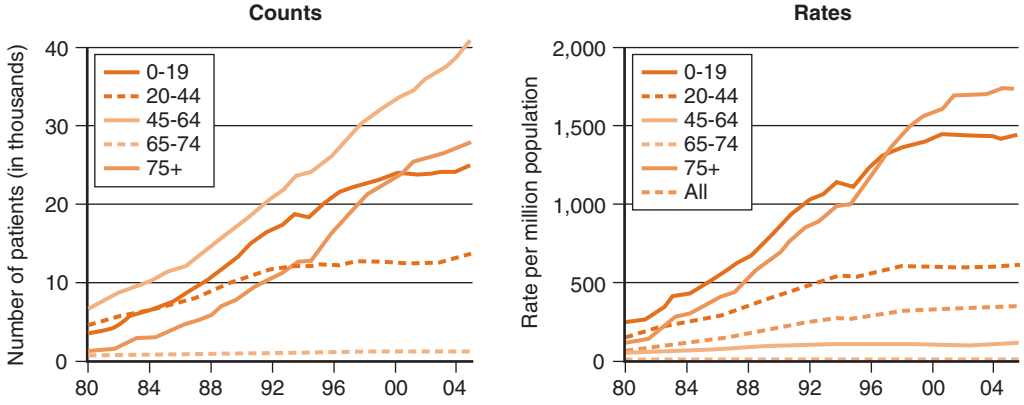


FIGURE 1-5 Incident counts and adjusted rates for ESRD in the United States, by age. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 2.5. atlas of end-stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

of ESRD due to glomerulonephritis continues to fall and was 26 per million population in 2006. Racial and ethnic disparities in the incidence of ESRD persist. In 2006, the incidence for African Americans was 3.6 times higher (1010 per million population) and for Native Americans was 1.8 times higher (489 per million population) compared to whites. Similarly, among Hispanics the incidence of ESRD (520 per million population) was 1.5 times greater than the non-Hispanic population.

Prevalence of End-Stage Renal Disease

At its inception, ESRD was expected to plateau at 40,000 prevalent patients, a number that was reached over 20 years ago. In 2006, 506,256 persons received renal replacement therapy, reflecting an age, gender, and race adjusted prevalence of 1626 per million population (Figure 1-6). This prevalence represents a 2.3% increase since 2005 and a 15% increase since 2000. This rise in prevalence has stabilized in the past 5 years. The median age of the prevalent ESRD persons continues to increase and was 58.8 years in 2006 (Figure 1-7). The gender and race adjusted prevalence of ESRD has increased the greatest among persons aged 65 to 74 years reaching 5700 per million population, reflecting a 20% increase since 2000 and a 48% increase since 1996. Numerically the largest single age group receiving renal replacement therapy is those aged 45 to 64 years. For persons aged 75 and older, the prevalence is 5000 per million population, and this prevalence is 23.6% higher than in 2000. Prevalent ESRD rates continue to reflect the race and ethnic disparities observed with incident ESRD. In 2006, prevalence of ESRD was 5004 per million population in African Americans, 2691 per million population in Native Americans, 1831 per million population among Asians, and 1194 per million population among whites. Diabetic ESRD continues to be the leading cause for prevalent ESRD patients (604 per million population) followed by hypertension and glomerulonephritis.

Global Perspectives on the Incidence and Prevalence of End-Stage Renal Disease

The USRDS 2008 ADR includes data on incidence and prevalence of ESRD from 44 countries and regions that voluntarily provide registry data to the USRDS. ESRD incidence and prevalence varies widely between countries (Figures 1-8 and 1-9). Incidence for reported ESRD is the highest in Taiwan at 418 per million population, followed by the United States. Incidences below 100 per million population are reported from a number of countries including Bangladesh, Pakistan, Russia, Philippines, Finland, and Norway. The highest prevalence of ESRD is also reported by Taiwan at 2226 per million population, followed by the United States and Japan. Clearly, factors beyond progression to advanced kidney failure play an important role in these estimates. There are differences in completeness and accuracy of data across regions and differences in resources and access to care. As a result, these comparisons must be performed with caution.

Perspective on the global trends in ESRD care is also provided by survey data reported by Fresenius Medical Care, a worldwide dialysis company. Grassmann and colleagues reported the results of survey data from 122 countries with established dialysis programs.[68] These countries represented 92% of the world population, and the report focused on treated ESRD patients at the end of 2004. Globally, 1.783 million persons received treatment for ESRD in 2004, reflecting an overall prevalence of 280 per million people worldwide. The prevalence was reported to be the highest in Japan (2045 per million population), followed by the United States. The lowest prevalence (70 per million population)

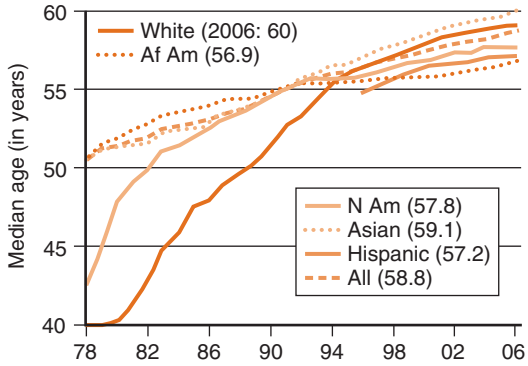


FIGURE 1-7 Median age of prevalent ESRD patients in the United States. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 2.17. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

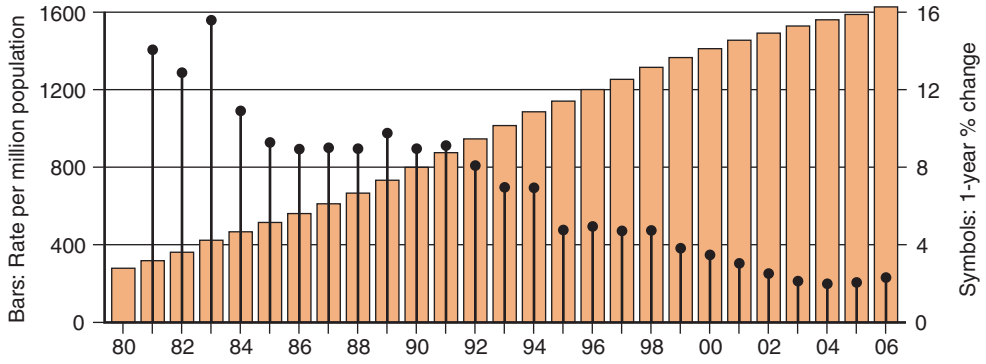


FIGURE 1-6 Adjusted U.S. prevalent rates of ESRD and annual percent change. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 2.11. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

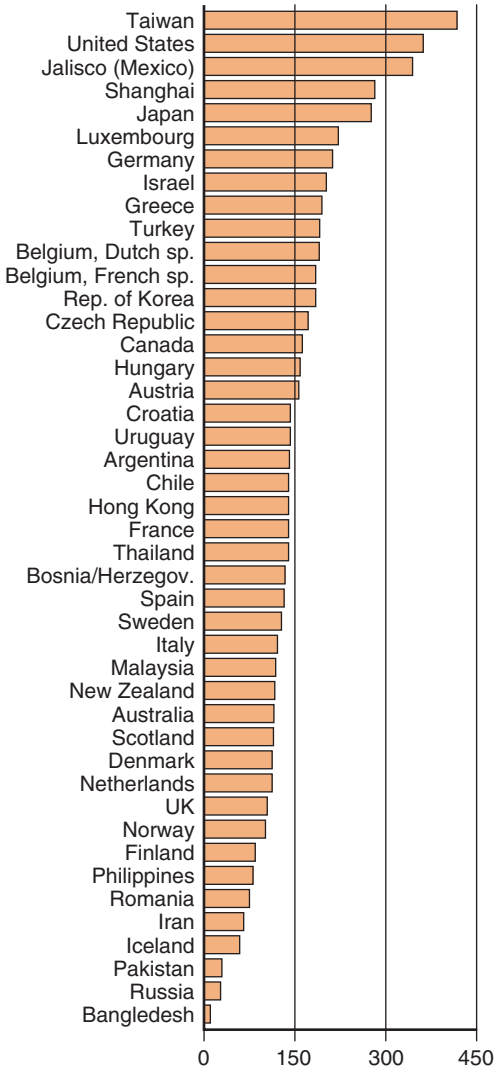


FIGURE 1-8 International comparison of ESRD incidence rates. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 12.2. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

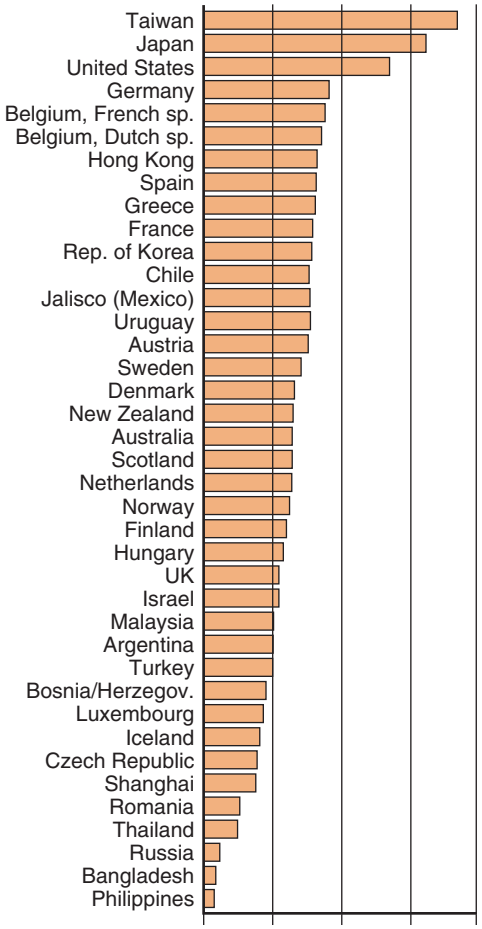


FIGURE 1-9 International comparison of ESRD prevalence rates. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 12.4. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

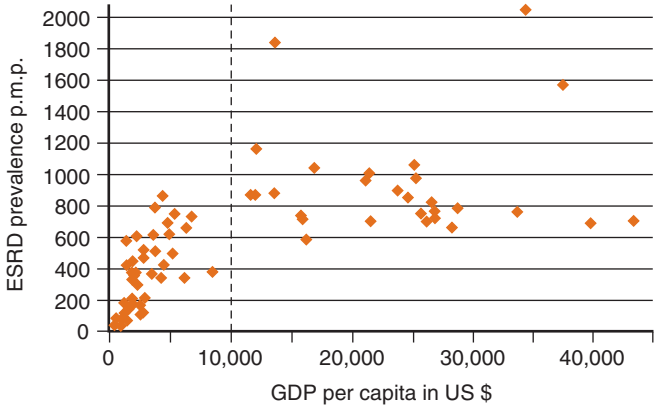


FIGURE 1-10 Prevalence of ESRD in 2004 versus economic welfare in the 75 countries with the largest ESRD populations. (From A. Grassmann, S. Gioberge, S. Moeller, G. Brown, ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends, Nephrol. Dial. Transplant. 20 [12] [2005] 2587-2593.)

was reported from Africa and rest of Asia, excluding Japan. The global prevalence numbers were 20% higher than an earlier survey using similar methodology performed in 2001. National economic strength appeared to be correlated with ESRD prevalence especially in countries with a Gross Domestic Product (GDP) per capita per annum below $10,000 (U.S. GDP for 2004 was $37,800 per capita), where access to dialysis is often limited. At higher GDPs, there did not appear to be a correlation suggesting factors other than economy may be playing a role in the prevalence of treated ESRD (Figure 1-10).

COSTS OF CHRONIC KIDNEY DISEASE

The K/DOQI classification has allowed better description of the costs associated with care of CKD patients not on dialysis. The new CKD diagnostic billing codes introduced in 2006 have allowed improved enumeration of costs using healthcare databases. Costs for CKD care can be divided into costs for CKD patients not on renal replacement therapy, costs during transition to renal replacement therapy, and ESRD costs.

Chronic Kidney Disease (Not on Dialysis) Costs

CKD is highly associated with diabetes, hypertension, obesity, cardiovascular disease, and stroke. In addition, patients with CKD are at higher risk of renal and nonrenal complications due to treatment of these disorders. As a result, the cost of care of patients with CKD is expected to be high. In an analysis of healthcare costs and resource use for 13,796 Kaiser Permanente Northwest Region health maintenance organization members and their age- and gender-matched controls followed for up to 5.5 years (June 2001), patients with CKD and no comorbidities had medical costs averaging $18,000 compared to $9800 among non-CKD patients without comorbidities.[69] The increment in costs for a patient with comorbidities was greater in those with than without CKD.

The 2008 USRDS ADR also reports the economic impact of CKD using the Medicare and Employee Group Health Plan (EGHP) data. In general, the EGHP costs are higher, reflecting cost shifting from Medicare and the lower ability of the private payors to set fees compared to Medicare. In 2006, CKD costs for Medicare patients exceeded $49 billion and represented 24.5% of the general Medicare costs. These costs have increased fivefold since 1993. The overall per patient per month costs are $2289 for dually-enrolled (Medicare and a secondary insurance) patients compared to 1,889 for Medicare enrollees and $2274 for the younger EGHP patients. These costs are several fold higher than the per patient per month cost of care for non-CKD patients with Medicare ($697 in 2006). CKD also has a multiplier impact on healthcare costs (Figure 1-11). The per patient per month costs in persons with CKD, diabetes, and congestive heart failure were $2973; twofold higher than in those with CKD alone ($1232).

Costs during Transition from Chronic Kidney Disease to End-Stage Renal Disease

The period of transition of care from CKD to ESRD is associated with high morbidity and mortality, which is reflective in the cost of care of these patients. The per patient per month costs rise dramatically during this transition period (Figure 1-12). The overall transition costs for Medicare patients increase from $6701 in the month prior to initiation of dialysis to $14,461 following initiation. Of this first month cost, $9588 (66.3%) is due to inpatient hospitalization; cardiovascular ($3478) and vascular ($1509) hospitalizations account for 52.7% of the total inpatient costs. The hospital use for ESRD patients is significantly higher in the first 3 months, and the presence of ischemic heart disease, late nephrologist referral, and use of temporary vascular access for dialysis are risk factors for increased hospital days.[70] Similar trends have been reported in other studies. In a study of ESRD in France, the mean duration of hospitalization at dialysis initiation was 30 days in late referred patients compared to 8 days for those referred at least 6 months prior to initiation, resulting in an excess cost of approximately 30,000 Euros per patient.[71] Similar findings were reported in a Scandinavian study; the duration of hospitalization was 31 days in the late referral population compared to 7 days in those referred early.[72] These data strongly support an advantage for early referral, but the ability to control for all factors that differ between the groups is limited. For example, acute kidney injury in the setting of

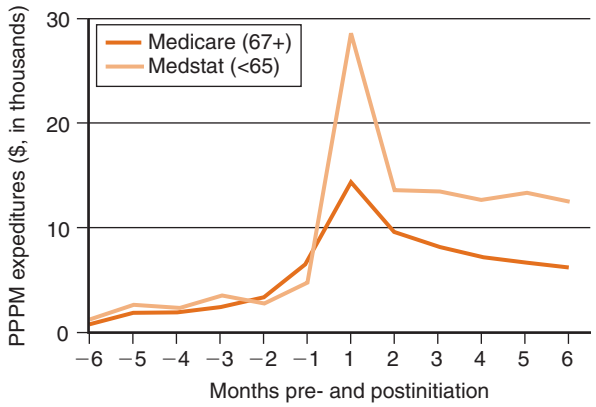


FIGURE 1-12 Total per patient per month costs in the transition to ESRD. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 11.9. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

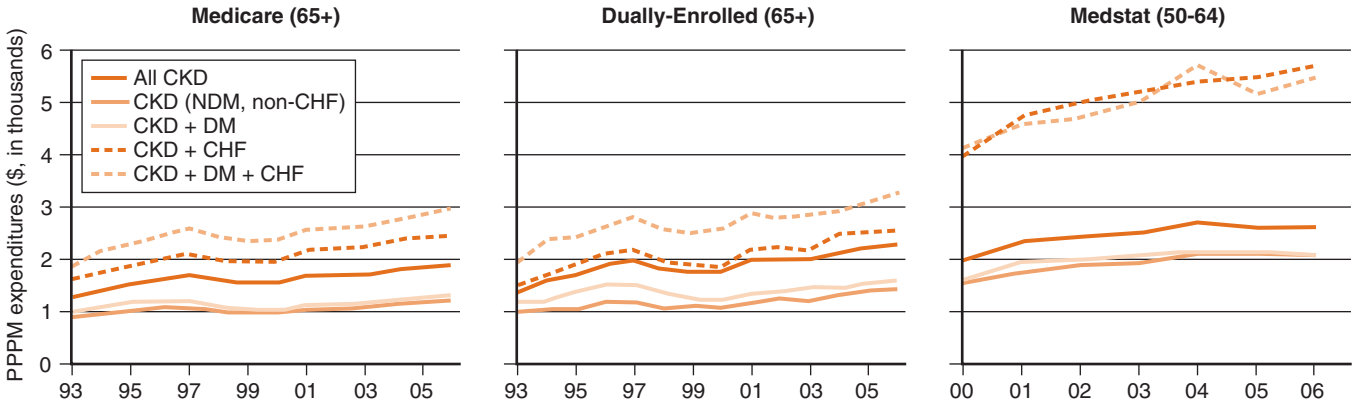


FIGURE 1-11 Per person per month CKD expenditures in the United States, by diagnosis and dataset. For comparison, the cost for Medicare enrollees without CKD is $697 per patient per month. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 1: Figure 5.4. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

CKD may lead to initiation of dialysis without the opportunity for early referral. Additional cost-effective analyses and, if possible, clinical trials of programs incorporating early referral and improved CKD care are needed.

End-Stage Renal Disease Costs

Costs of renal replacement therapy include expenses of the dialysis treatment (peritoneal or hemodialysis); creation of access for dialysis treatment; hospitalizations due to cardiovascular, infectious, and access-related complications; transplant related costs including costs of organ procurement, surgery, and immunosuppression; and costs of medications used for treatment of anemia (erythropoietin supplementation agents [ESAs] and iron) and hyperparathyroidism (vitamin D analogues). The high disease burden of this population contributes to the high healthcare resource use.

In 2006, ESRD costs as determined by Medicare spending were $23 billion or 6.4% of the Medicare budget. Although the ESRD costs continue to increase, they have remained at a stable 6.3% to 6.5% of the Medicare budget. Of the total Medicare costs (Figure 1-13), three-quarters are spent on inpatient (38.5%) and outpatient care (34.6%). Per patient per year costs for hemodialysis were $71,889 in 2006, compared to $53,327 for peritoneal dialysis and $24,951 for kidney transplantation. Among dialysis patients, those with catheters and grafts have the highest per person per year costs, at $77,093 and $71,616, respectively, whereas $59,347 and $53,470 are spent annually on those with arteriovenous (AV) fistulas and peritoneal dialysis catheters, respectively. These costs were much higher for non-Medicare providers. The effect of comorbidities in contributing to these high costs is illustrated by the costs for inpatient and outpatient services for diabetics versus nondiabetics; the costs for diabetics ($54,936 per year) was 25% greater than the $43,920 per year costs incurred by nondiabetic patients. ESAs account for approximately 10% of the Medicare spending, but the rise in ESA costs has plateaued. Per patient per year costs for injectable vitamin D therapy was approximately $2000, and the cost for intravenous iron was approximately $700. The costs for vascular access infections were the highest for those with catheters at $2500 compared to $775 for those with an arteriovenous graft and $240 for those with a fistula.

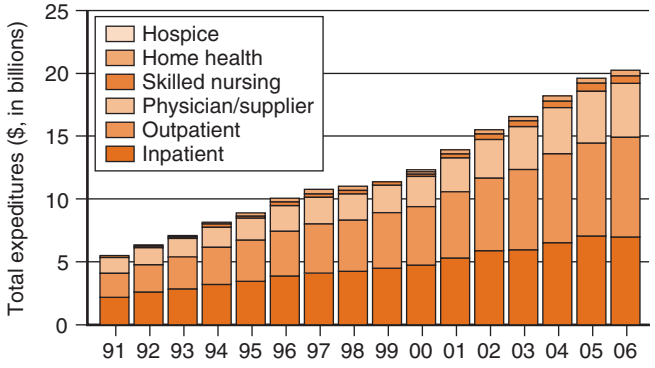


FIGURE 1-13 Total medicare dollars spent on ESRD, by type of service. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 11.6. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

International comparison of ESRD costs is more problematic due to the vastly different healthcare systems, funding sources, accounting methods, access to care, costs of hospitalization and medications, and societal norms.[73] The economic burden of ESRD in Canada in 2000 was estimated to be $1.9 billion with a per patient per year cost of $51,099.[74] United Kingdom hemodialysis costs for 2005 were estimated to be approximately $18,000 per person per year but did not include the cost of medications.[75] In Sweden in 2002, the cost of hemodialysis was $70,796 per person per year.[76] In Spain during 2003, the cost of hemodialysis per patient per year was estimated to be $46,327.[77] The annual expenditure per ESRD patient in Japan was estimated to be $41,681.[78] In New Zealand, where ESRD care has always been "rationed," the 2003 ESRD expenditures were $23,372 per person per year.[79] In Australia, the total annual expenditure per ESRD patient per year in 2006 was estimated to be $36,917.[80] A comparative review of healthcare systems and ESRD costs in 12 countries was performed as part of the International Study of Health Care Organization and Financing, a substudy within the Dialysis Outcomes and Practice Patterns Study (DOPPS).[81] A moderate correlation ($p = 0.70$) was noted between the annual healthcare expenditures per capita and the annual expenditure per ESRD patient but appears to be significantly influenced by the U.S. healthcare spending (Figure 1-14).

OUTCOMES OF CHRONIC KIDNEY DISEASE

CKD is progressive disorder associated with a myriad of complications. Some of these complications are direct consequences of loss of kidney function such as volume overload, hyperkalemia, hyperphosphatemia, metabolic acidosis, secondary hyperparathyroidism, anemia, and hypertension. Many complications are also the results of treatment of causes of CKD as in the case of chemotherapy for glomerulonephritis. Ultimately, CKD progression to ESRD is an important outcome. Table 1-5 provides a conceptual overview of some of the most common outcomes whose risk is elevated by

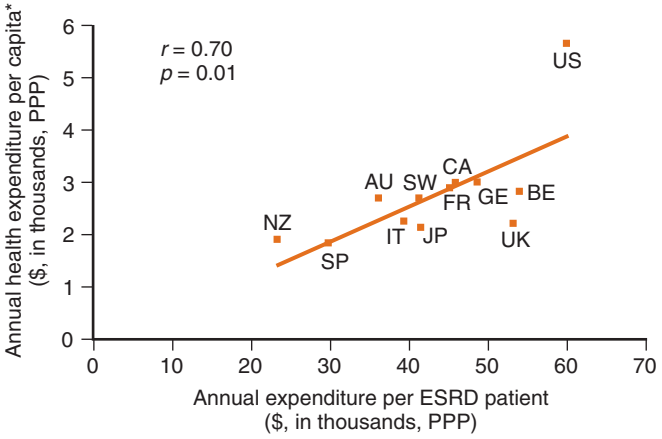


FIGURE 1-14 Annual expenditure per ESRD patient and general population health expenditure per capita. (From A. Dor, M.V. Pauly, M.A. Eichleay, P.J. Held, End-stage renal disease and economic incentives: the International Study of Health Care Organization and Financing [ISHCOF], Int. J. Health Care Finance Econ. 7 [2-3] [2007] 73-111.)

TABLE 1-5 Risk Factors for Progression of Chronic Kidney Disease (CKD), Cardiovascular Disease (CVD), and Death

OUTCOME	IMPORTANCE FOR DIFFERENT OUTCOMES		
	CKD STAGE	*TYPE OF KIDNEY DISEASE (DIAGNOSIS)*[a]	*PROTEINURIA*
Concurrent complications[b]	+++	+	+
Prognosis (next 10-years)			
Risk of CVD or mortality	+++	+	+++
Risk of kidney failure	+++	++	+
Rate of decline in GFR	+	+++	++

GFR, glomerular filtration rate.
Modified and reprinted with permission [16].
[a]For example, diabetic kidney disease, glomerular diseases, vascular diseases (such as hypertensive nephrosclerosis), tubulointerstitia! disease (including disease due to obstruction, infection, stones, and drug toxicity or allergy), and cystic disease (including polycystic kidney disease).
[b]Concuirent complications include hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life.
(Adapted from A.S. Levey, K.U. Eckardt, Y. Tsukamoto, et al., Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes [KDIGO], Kidney Int. 67 [6] [2005] 2089-2100.)

CKD.[10] It is important to note that markers of severity such as eGFR and albuminuria have a different importance for different outcomes. In addition, risk of different outcomes will depend on a range of other covariates including some that are not CKD measures such as age, sex, and others that relate to CKD but have a strong additional effect such as hypertension and heart failure. Communicating a full picture of prognosis in CKD without making a system that is too complex to be useful is a major challenge. Discussion of all these complications is beyond the scope of this chapter. Instead, we will focus on the epidemiological associations between CKD (not on dialysis), cardiovascular disease, and related morbidity and mortality, including the potential prognostic role of albuminuria. We will then review the morbidity and mortality associated with ESRD.

Glomerular Filtration Rate and its Association with Outcomes in Chronic Kidney Disease

Large epidemiological studies have demonstrated the increased risk of mortality with reduced level of GFR. In a study of over 1 million individuals from the Kaiser Permanente Renal Registry, there was a graded increase in the risk of all cause and cardiovascular mortality with lower levels of GFR.[82] Compared to individuals with eGFR greater than 60 ml/min/1.73 m^2, the adjusted risk of death was 20% higher among individuals with eGFR of 45 to 59 ml/min/1.73 m^2, 80% higher among those with eGFR of 30 to 44 ml/min/1.73 m^2, 3.2-fold higher among those with eGFR of 15 to 29 ml/min/1.73 m^2 and 5.9-fold higher with eGFR less than 15 ml/min/1.73 m^2. This graded risk was seen despite the limited standardization of creatinine across laboratories. In another study that included 22,634 participants of four community-based longitudinal studies, the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study, individuals with an eGFR less than 60 ml/min/1.73 m^2 had a 19% higher risk of all-cause mortality compared to those with a higher eGFR.[83] A systematic review of 39 studies that followed 1.371 million participants also demonstrated similar findings of increased all-cause mortality risk with CKD.[84]

An important aspect of the mortality associated with CKD is the impact of age. In a study of 209,622 U.S. veterans with CKD stages 3 to 5 followed for a mean of 3.2 years, the risk of ESRD increased with lower GFR at all ages.[85] The risk of mortality, however, increased with age even faster such that the threshold eGFR where the risk of ESRD exceeded risk of mortality was 45 ml/min/1.73 m^2 in those aged fewer than 45 years, 30 ml/min/1.73 m^2 for those aged 45 to 64 years, and 15 ml/min/1.73 m^2 for those aged 65 to 84 years. For individuals older than 85 years, the risk of death exceeded risk of ESRD even at eGFR less than 15 ml/min/1.73 m^2. The impact of older participants being less likely to initiate renal replacement therapy is unknown, and the risk of other complications of CKD in older age is important to quantify.

There is no question that CKD is associated with increased cardiovascular risk. Much of this risk, however, is related to the high prevalence of CKD and cardiovascular disease risk factors. Because CKD aggravates many risk factors including hypertension and left ventricular hypertrophy (LVH), separating the risk related to CKD alone is difficult.

The high prevalence of cardiovascular disease in patients with CKD results in significant morbidity and mortality attributable to cardiovascular disease. For example, the prevalence of LVH increases with declining levels of kidney function. In a study of 175 patients in a CKD clinic, the prevalence of LVH measured by echocardiography increased from 27% to 31% to 45% with lowering of creatinine clearance from more than 50 ml/min to 25 to 50 ml/min to less than 25 ml/min, respectively.[86] In moderate CKD, most cardiovascular risk factors were risk factors for subsequent events.[87]

A summary statement of The American Heart Association concluded that CKD appears to be an independent risk factor for cardiovascular disease and reinforced the National Kidney Foundation guidelines for early recognition and treatment of CKD and screening individuals with cardiovascular disease for the presence of CKD.[88] In 4893 participants of the Cardiovascular Health Study, each 10 ml/min/1.73 m^2 lower eGFR was independently associated with a 5% higher risk of de novo cardiovascular disease and 7% higher risk of recurrent cardiovascular disease.[89] Many additional studies have documented similar risk, although the number of studies that relate risk to both estimated GFR and albuminuria is limited.

Stronger associations are noted between CKD and cardiovascular disease using cystatin C as a marker of GFR and kidney function. In a study of 4637 participants of the Cardiovascular Health Study, higher cystatin C levels were associated with increased cardiovascular and all-cause mortality. The highest quintile of cystatin C ($\geq$ 1.29 mg/L) compared to the lowest two quintiles ($\leq$ 0.99 mg/L) was associated with 2.3-fold higher risk of cardiovascular death and a 48% higher risk of myocardial infarction and stroke.[90] In 3044 participants of the Health, Aging, and

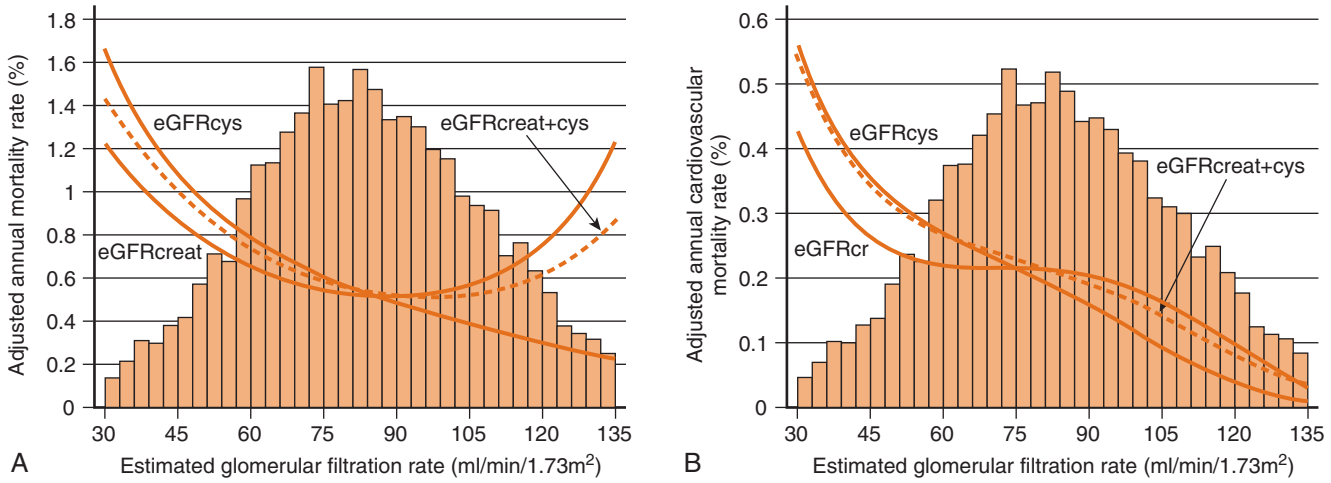


FIGURE 1-15 Adjusted annual rate, by estimated glomerular filtration rate (eGFR) of all-cause mortality (A) and cardiovascular mortality (B). eGFRcys: estimated GFR based on cystatin C, age, sex, and race; eGFRcreat: estimated GFR based on serum creatinine, age, sex, and race; eGFRcreat+cys: estimated GFR based on serum creatinine, cystatin C, age, sex, and race. Incidence rates were adjusted to the incidence rate of a white female with the lowest risk category for categorical covariates (smoking status, diabetes status, previous cardiovascular disease, C-reactive protein category, and blood pressure category) and the overall mean values of continuous covariates (age, body mass index, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol, log triglycerides). *Vertical bars* represent histogram of the mean of all three GFR estimates. (From B.C. Astor, A.S. Levey, L.A. Stevens, F. Van Lente, E. Selvin, J. Coresh, Method of Glomerular Filtration Rate Estimation Affects Prediction of Mortality Risk, J Am Soc Nephrol. 20 [10] [2009] 2214-2222.)

Body Composition study, a cohort of well-functioning elderly participants aged 70 to 79 years, the risk of cardiovascular death was twofold higher (adjusted hazard ratio [HR], 2.24; 95% Confidence Interval [CI], 1.30-3.86) in those with a high cystatin C ($\geq$ 1.19 mg/L) than in those with a low cystatin C ($<$ 0.84 mg/L).[91] In addition, it is clear that eGFR from cystatin C results in a more linear risk gradient than serum creatinine. The nonlinearity is more dramatic for total mortality (U-shape) than cardiovascular mortality, and recent data suggest that equations that combine serum cystatin and creatinine may suffer the limitations of estimates based on creatinine (Figure 1-15).[92] Presumably, the nonlinearity is due to limitations of creatinine at higher eGFR and confounded by muscle wasting rather than a unique advantage of cystatin C.[93]

The 2008 USRDS ADR provides information on hospitalization in diagnosed CKD patients that are eligible for Medicare.[32] Congestive heart failure hospitalizations are six times higher in CKD patients and hospitalization for atherosclerotic heart disease is twice as high in CKD patients compared to non-CKD patients. Similarly, infectious complications such as pneumonia occur two to four times as frequently in CKD patients compared to non-CKD patients.[32]

Data on other outcomes will not be summarized. However, it is noteworthy that the presence of CKD is also a risk factor for development of acute kidney injury. In a study comparing 1746 hospitalized members of Kaiser Permanente who developed dialysis-requiring acute kidney injury with 600,820 hospitalized members who did not, the adjusted risk of acute kidney injury was twofold, sixfold, 29-fold, and 40-fold higher for those with baseline eGFR of 45 to 59, 30 to 44, 15 to 29, and less than 15 ml/min/1.73 m^2, respectively, compared to those with eGFR greater than or equal to 60 ml/min/1.73 m^2.[94] Risk on medication toxicity and other preventable outcomes is limited.

Albuminuria and its Association with Outcomes in Chronic Kidney Disease

The normal rate of albumin excretion is less than 20 mg/day, and persistent values between 30 and 300 mg/day are referred to as microalbuminuria. Using the urinary albumin-to-creatinine ratio, a value above 30 mg/g (or 0.03 mg/mg) corresponds to microalbuminuria. Albuminuria is defined as persistent albumin excretion of greater than 300 mg/day. Albuminuria is strongly associated with progression to ESRD in multiple studies among both patients with CKD and general population samples.[95–98] In the 12,866 participants of the Multiple Risk Factor Intervention Study, followed for 25 years for development of ESRD, dipstick proteinuria of 1+ was associated with threefold higher risk, greater than or equal to 2+ proteinuria with 16-fold higher risk, and a combination of eGFR less than 60 ml/min/1.73 m^2 and greater than or equal to 2+ proteinuria was associated with a 41-fold higher risk of ESRD.[96] The risk of progression to kidney failure was recently assessed in 65,589 participants of the Nord-Trøndelag Health (HUNT II) Study in Norway.[99] Interestingly, 58 patients started renal replacement therapy and 132 others died of advanced CKD (documented stable eGFR less than 15 or other indication for renal replacement therapy), suggesting that it is important to look at all kidney failure beyond those accepting renal replacement therapy. The risk of kidney failure was very strongly related to both albuminuria and eGFR with relative risks of greater than 1000 (Table 1-6).

Several studies have demonstrated the strong association between microalbuminuria and cardiovascular disease morbidity and mortality in patients with and without diabetes. In 9043 participants of the Heart Outcomes Prevention Evaluation (HOPE) study who were followed for a median of 4.5 years, the presence of microalbuminuria was associated with an 83% higher risk of cardiovascular events (myocardial infarction, stroke, or cardiovascular death) and a threefold

TABLE 1-6 Hazard Ratios for Progression to ESRD by Categories of eGFR and Albumin to Creatinine Ratio[a]

PARAMETER	eGFR (ml/min per 1.73 m²)			
	≥60	45 to 59	30 to 44	15 to 29
Normal ACR				
Unadjusted	1[b]	30.8 (9.3 to 102.2)[b]	76 (18.5 to 313.2)[b]	583.1 (120.5 to 2822)[c]
Adjusted	1[b]	23.4 (6.7 to 82.1)[b]	51.9 (11.5 to 233.5)[b]	368.7 (69.2 to 1964)[c]
Microalbuminuria				
Unadjusted	33.9 (11.2 to 102.6)[b]	227.4 (72.8 to 710.2)[c]	740.6 (246.7 to 2222)[c]	3833 (1265 to 11,611)[d]
Adjusted	27.3 (8.8 to 84.5)[b]	146.5 (42.7 to 502.7)[c]	448.9 (133.7 to 1508)[c]	2202 (632.5 to 7669)[d]
Macroalbuminuria				
Unadjusted	306.6 (50.3 to 1871)[c]	1108 (285.8 to 4297)[c]	3167 (1066 to 9403)[d]	6957 (2286 to 21,165)[d]
Adjusted	196.3 (27.6 to 1397)[c]	641.1 (143.6 to 2862)[c]	2036 (594.3 to 6973)[d]	4146 (1187 to 14,482)[d]

[a]Numbers are unadjusted heart rate (95% CI) and HR after adjustment for age. gender, systolic blood pressure. antihypertensive medication, diabetes. HDL cholesterol, and physical activity in a Cox regression analysis. Microalbuminuria was ACR ranging from 20 to 200 mg/g in men and 30 to 300 mg/g in women.
[b]Low risk for progression to ESRD.
[c]Medium risk for progression to ESRD.
[d]High risk for progression to ESRD.
(Adapted from S.I. Hallan, E. Ritz, S. Lydersen, et al., Combining GFR and albuminuria to classify CKD improves prediction of ESRD, J. Am. Soc. Nephrol. 20 [5] [2009] 1069-1077.)

higher risk for hospitalization.[100] In the 8206 participants of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, albuminuria was associated with increased cardiovascular risk independent of the level of blood pressure.[101] Similar findings have been noted in several epidemiological studies. In the 85,421 participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study in Netherlands, a twofold increase in urine albumin concentration in a spot specimen was associate with a 29% increase in cardiovascular mortality.[12] In a 10-year prospective cohort study of 30,764 men and 60,668 women aged 40 to 79 years who participated in annual health checkups in 1993, dipstick-positive proteinuria was associated with a 38% and 2.2-fold higher risk of cardiovascular death among men and women, respectively.[102]

PREVEND investigators also compared albuminuria as assessed by 24-hour urine collection versus spot specimen from first morning void (urinary albumin concentration or urine albumin-to-creatinine ratio) in predicting cardiovascular morbidity and mortality.[103] The area under the receiver operating characteristic curve was very similar for the three measures; 0.65, 0.62, and 0.66 for 24-hour urine, urine albumin concentration, and urine albumin-to-creatinine ratio, respectively. These findings suggest that first morning void spot urine measurements are a good alternative to 24-hour urine collections for cardiovascular disease risk stratification. A recent analysis reported the risk of cardiovascular mortality using the linked mortality of NHANES that includes 13-year follow-up data (from 1988 to 2000).[104] Within each category of eGFR (≥ 90, 60 to 89, and 15 to 59 ml/min/1.73 m²) and albuminuria (< 30, 30 to 299, and ≥ 300 mg/g), there was a graded increase in cardiovascular and all-cause mortality. There was a fourfold increase in cardiovascular mortality in individuals with albuminuria (≥ 300 mg/g) and eGFR < 90 ml/min/1.73 m² compared to individuals with eGFR ≥ 90 ml/min/1.73 m² and no microalbuminuria (Figure 1-16). These findings of increased risk were consistent across all racial/ethnic groups and in both men and women.

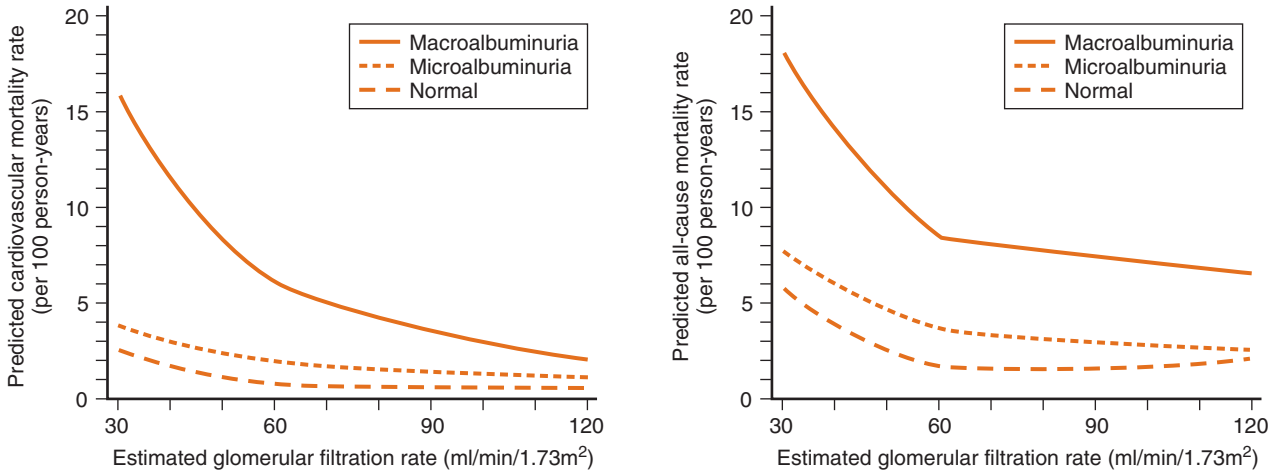


FIGURE 1-16 Predicted incidence rate of cardiovascular (*left*) and all-cause (*right*) mortality associated with estimated glomerular filtration rate, by category of albuminuria, Third National Health and Nutrition Examination Survey, 1988–2000. Rates were adjusted to the mortality rate of a 60-year-old non-Hispanic in white male and were calculated using smoothed linear splines with knots at 60, 75, and 90 ml/minute/1.73 m². Knots that did not significantly improve the fit of the model ($p > 0.15$) were removed. (From B.C. Astor, S.I. Hallan, E.R. Miller III, E. Yeung, J. Coresh, Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population, Am. J. Epidemiol. 167 [10] [2008] 1226-1234.)

End-Stage Renal Disease Outcomes

Overall survival with ESRD remains dismal, though improvement in survival after the first year of ESRD has occurred steadily over the last decade. The first-year survival on hemodialysis, however, remains poor with an expected mortality rate of 23 per 100 person-years. The first year mortality rates have fallen 30% since 1998 for peritoneal dialysis patients, 16% for transplant patients, but only 5.3% for hemodialysis patients. This high first-year mortality rate for hemodialysis patients partly reflects the presence of other comorbidities; the sickest of all patients and those without prior nephrologist care are more likely to be started on hemodialysis. The 5-year survival probabilities for 1997 to 2001 incident ESRD patients were 35% overall, 31% for hemodialysis, 29% for peritoneal dialysis, and 69% for transplants. This 5-year survival probability on dialysis is worse than the 5-year survival probabilities for breast cancer (88%), colon cancer (64%), HIV seroconversion (95%), and AIDS (90%).[60,105–107] The all-cause mortality rates in dialysis patients, 174 per 1000 person-years in 2006, was eight times higher than the general Medicare population. Transplant patients have relatively better survival, with 20% and 60% higher mortality than the general population in those age 20 to 44 years and greater than 44 years, respectively (Figure 1-17). Comorbidity rates, however, vary dramatically across these groups. The overall and cause-specific mortality rates for incident dialysis patients peaks at 412 per 1000 person-years at the third month after dialysis initiation followed by a decline reaching 218 per 1000 person-years by the twelfth month. Cardiovascular disease and infection-related deaths are the leading causes of death and follow the same pattern as overall mortality. Hospitalization rates are high in ESRD patients, as expected, compared to the general population.

More than 50% of deaths in patients on dialysis are likely to be due to cardiovascular disease.[108] Atherosclerotic cardiovascular disease is present in more than 50% of dialysis patients; more than 80% have hypertension, 74% have left ventricular hypertrophy (LVH) and, 30% to 40% have congestive heart failure (CHF).[109–116] In incident dialysis patients, baseline CHF is associated with a 40% mortality in the first year, and CHF hospitalization is associated with an 8% inpatient, 54% 1-year, and 80% 5-year mortality.[32,115,117] Other risk factors of death in dialysis patients include volume overload and hypertension, elevated calcium and phosphate, anemia, malnutrition, and incomplete removal of uremic toxins.[118–121]

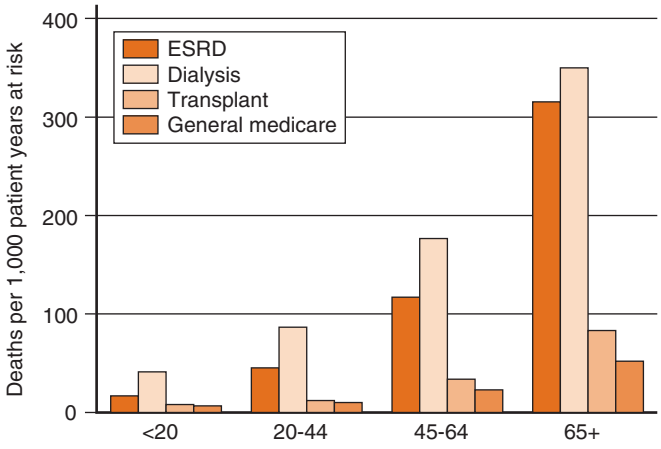


FIGURE 1-17 All-cause mortality of ESRD patients compared to general medicare population, by age. (Data from U.S. Renal Data System, USRDS 2008 Annual Data Report: Volume 2: Fig 6.8. Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008. Available online at: http://www.usrds.org/adr.htm. Last accessed 6/24/2010.)

In addition to traditional risk factors, a wide array of novel cardiovascular risk factors have been implicated in the high all-cause and cardiovascular mortality seen in dialysis patients.[88] Most of the traditional cardiovascular disease risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low HDL cholesterol, are highly prevalent in ESRD patients. Several putative nontraditional factors, such as hyperhomocysteinemia, oxidant stress, dyslipidemia, elevated inflammatory markers, oxidant stress, anemia, and abnormal calcium and phosphorus metabolism may also be contributing to this increased risk.[88] Clinical trials focusing on these traditional markers have, however, failed to demonstrate any significant reduction in mortality. In the recently published, An Assessment of Survival and Cardiovascular Events (AURORA) trial, there was no effect on mortality of hemodialysis patients despite a 43% reduction in LDL cholesterol levels, mirroring findings of an earlier trial, the Die Deutsche Diabetes Dialyse Studie (the 4D study).[122] In the 4D Study, the risk of all cardiac events (death from cardiac causes, nonfatal myocardial infarction, coronary artery bypass graft surgery, and coronary angioplasty) was reduced by 18% (HR, 0.82; 95% CI, 0.68-0.99) but was offset by a twofold increase in risk of fatal stroke (HR, 2.03; 95% CI, 1.05-3.93).[123] The Study of Heart and Renal Protection (SHARP) has randomized 9000 patients with CKD (3000 on dialysis) in 300 hospitals and 20 countries to cholesterol lowering therapy with a combination of simvastatin and ezetimibe. The study takes into account the complexity of cardiovascular disease in CKD where nonatherosclerotic factors also play an important role and benefits of a single drug therapy are likely to be more modes. The study is expected to complete in July 2010.[124]

CONCLUSION

The last decade has seen a major change in our understanding of the epidemiology of CKD, driven to a major extent by the classification system proposed by the K/DOQI group. Efforts are now being directed toward developing and evaluating strategies for screening populations at high risk of CKD and refining risk factors for CKD prognosis. A KDIGO Controversies Conference held in 2009 gathered evidence from the largest studies to examine how to optimally combine estimated GFR and albuminuria in determining prognosis and the mortality results from the general population have been recently published.[28] The best studied outcomes of CKD are mortality, cardiovascular disease, and ESRD, but the risks of CKD progression, acute kidney injury, hospitalization, and other complications are clearly important. As the population prevalence of CKD risk factors including diabetes, hypertension, and obesity increases, the prevalence of CKD and ESRD are also likely to increase.

Trends in CKD incidence are harder to track reliably but for ESRD are stabilizing. The overall survival of advanced kidney failure treated with dialysis remains quite dismal, and most recent trials of dialytic and nondialytic therapies have shown no improvement in survival. The modest improvement in care of dialysis patients with better control of biochemical parameters is probably offset with increasingly liberal criteria for acceptance into dialysis programs worldwide. Concerted efforts are needed to study and implement new paradigms of treatment to improve outcomes in patients with CKD and ESRD.

A full list of references are available at www.expertconsult.com.

Chapter 2

MEASUREMENT AND ESTIMATION OF KIDNEY FUNCTION

Lesley A. Stevens, M.D., M.S., Cindy Huang, M.D., Ph.D. and Andrew S. Levey, M.D.

The kidney performs specialized functions to maintain constancy of the internal composition of the body fluids. These functions include excretion of waste products, regulation of extracellular fluid volume and composition, production and catabolism of hormones, and regulation of acid–base balance. The normal kidney can adapt to wide variations in intake and in extrarenal loss of fluid and electrolytes through regulation of glomerular filtration and tubular reasbsorption and secretion. In this chapter, we focus on measurement and estimation of glomerular filtration as an index of overall kidney function.

GLOMERULAR FILTRATION: DERMINANTS AND MEASUREMENT

Definition and Normal Glomerular Filtration

The human kidney contains approximately 1 million glomeruli,[1,2] each approximately 150 to 200 microns in diameter. The total surface area provided for glomerular filtration approximates one square meter.[3] Approximately 180 liters per day (or 125 ml/min) of tubular fluid are produced from renal plasma flow by the process of ultrafiltration, driven by the high hydrostatic pressure across the glomerular capillaries and facilitated by the hydraulic permeability of the glomerular capillary wall that is one to two orders of magnitude greater than other capillaries.[4]

The glomerular filtration barrier is both size- and charge-dependent. Substances with molecular weights lower than 10,000 daltons freely pass the glomerular capillary wall.[5–7] Plasma proteins are excluded from the filtrate as a consequence of the structure of the glomerular capillary wall.

Determinants of Glomerular Filtration Rate

The glomerular filtration rate (GFR) is dependent on the number of nephrons (N) and the single-nephron glomerular filtration rate (SNGFR), as described here:

(Equation 1) $$GFR = N \times SNGFR$$

In normal individuals and in patients with kidney disease, in whom nephron number may be reduced, regulation of GFR occurs via regulation of SNGFR.

(Equation 2) $$SNGFR = K_f(\Delta P - \Delta \pi)$$

where

ΔP = the difference between the net transcapillary hydraulic pressure favoring filtration

$\Delta \pi$ = net oncotic pressure opposing filtration

Kf = the ultrafiltration coefficient, a composite measure of the surface area and permeability characteristics of the glomerular ultrafiltration barrier

ΔP is determined by the difference between the glomerular capillary hydraulic pressure and that in the earliest proximal tubule. Δπ is determined by the glomerular oncotic pressure alone as the ultrafiltrate is virtually protein-free. Absent from this equation is the renal plasma flow rate. Alterations in renal plasma flow affect SNGFR largely by influencing ΔP and Δπ.

Normal Range and Variability of Glomerular Filtration Rate

The GFR cannot be measured directly. Instead, as discussed later, it is estimated from the urinary clearance of an ideal filtration marker, such as inulin. Normal values show considerable variation among individuals, principally due to differences in age, sex, and body size. Hence, measured values of GFR are typically adjusted for body size and compared to normative values for age and sex.[8] A compilation of inulin clearance measurements in young adults shows the mean value in men to be 131 ml/min/1.73 m^2, and in women to be 120 ml/min/1.73 m^2[8,9](Figure 2-1), with considerable variation among individuals and over time. Some of these same factors also contribute to variation in GFR in patients with kidney disease.

1. *Sex and Body Size.* The GFR is related to glomerular surface area and kidney size.[10] Measured values for GFR are conventionally factored by 1.73 m^2, the mean body surface area of men and women 25 years of age. Nonetheless, as described previously, body surface-area adjusted values for GFR are approximately 8% higher in young men than in women of the same age. Recently, this has led to questioning about the appropriateness of the use of body surface area as the factor by which GFR is adjusted for body size.[11] Some have suggested that extracellular volume is a more appropriate index given that the purpose of GFR is to regulation body fluid composition.[12]
2. *Age.* Both cross-sectional and longitudinal studies show a decline in GFR of approximately 10 ml/min/1.73 m^2 per decade after the age of 30 years, such that during the 50 years from age 30 to age 80, normal GFR declines by almost 40%, from approximately 130 to 80 ml/min/1.73 m^2.[8,13,14] Age-related decline in GFR has been traditionally interpreted as a normal; however, other data suggest that there is considerable variation in age-related decline,[13,14] which means that it may be related to disease or other factors.[15]
3. *Pregnancy.* A marked increase in GFR occurs during pregnancy due to an increase in renal plasma flow and a decrease in plasma oncotic pressure.[10] GFR may increase up to 50% during the first trimester, persist at that level until term, and then return to normal approximately 4 to 8 weeks following the end of pregnancy. Pregnancy-induced hyperfiltration also occurs in women with preexisting chronic kidney disease, and the percentage increase appears proportionate to the prepregnancy level of GFR.
4. *Protein Intake.* The effect of protein intake on the GFR varies according to the duration of protein feeding (habitual protein intake vs. meat meals or amino acid

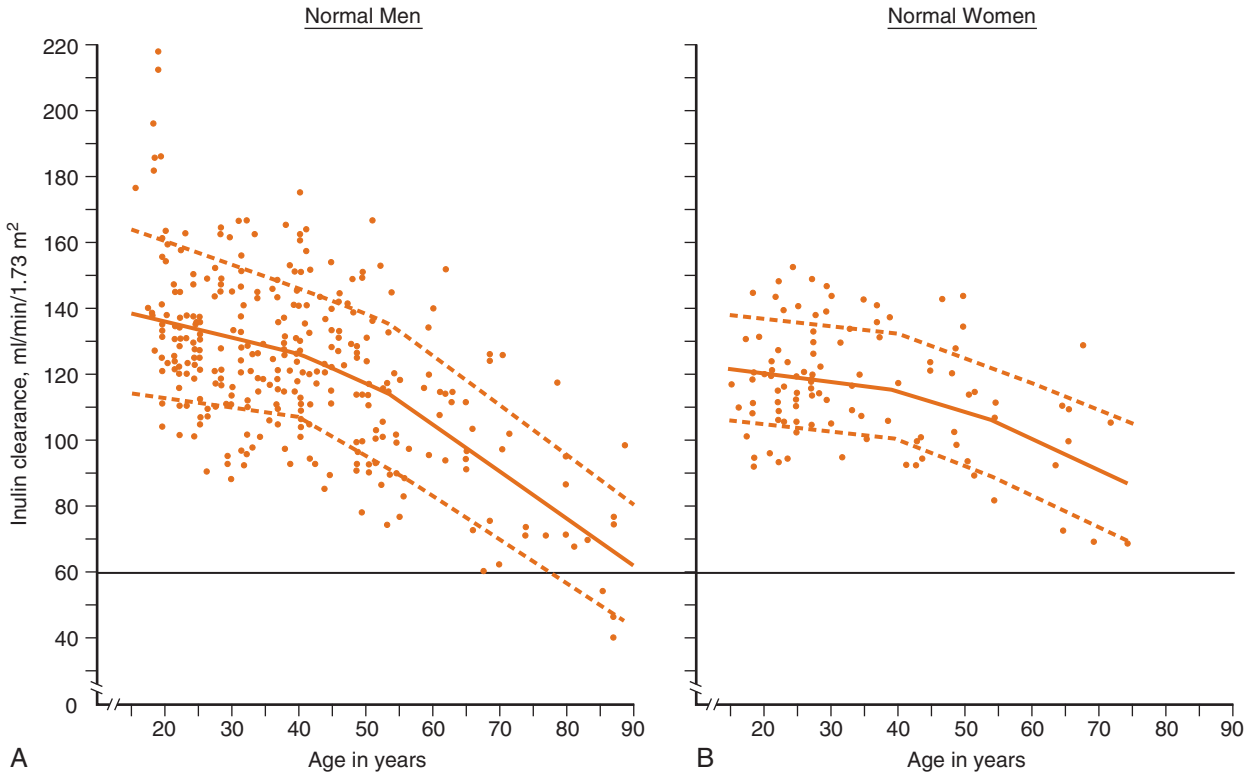


FIGURE 2-1 Normal Values for GFR in Men and Women. Normal values for inulin clearance are shown for men **(A)** and women **(B)** of various ages, with the GFR measured as the urinary clearance of inulin. A GFR value of 60 ml per minute per 1.73 m^2 is the threshold for the definition of chronic kidney disease. Solid lines represent the mean value of GFR per decade of age, and dashed lines represent the value 1 standard deviation from the mean value of GFR per decade of age. (From L.G. Wesson, Renal hemodynamics in physiological states. In: Wesson LG (ed). Physiology of the human kidney. New York: Grune and Stratton, 1969, 96-108.)

infusions), type of protein (animal vs. vegetable or soya protein sources; essential vs. nonessential amino acids).[16] After a meat meal, GFR and renal plasma flow rise within an hour and remain elevated for several hours. Similar increases in GFR and Renal Plasma Flow (RPF) were noted in participants fed high, medium, or low protein diet for 2 weeks. Some studies suggest a greater response to animal than vegetable protein in habitual diets and in response to protein loads. Conversely, long-term malnutrition is associated with reduced kidney size suggesting structural and hemodynamic alterations.

It had been proposed that protein-induced hyperfiltration represents "renal reserve capacity," which is lost prior to the reduction in baseline GFR associated with kidney disease. However, it has now been shown conclusively that changes in GFR occur in response to changes in habitual protein intake or meat meals in patients with kidney disease and reduced GFR and with animals with experimental kidney disease.

5. *Diurnal Variation.* GFR is approximately 10% higher in the afternoon than in the middle of the night, which may be related to the variation in protein intake or hydration during the day, or to transient reductions in GFR associated with exercise.[10]
6. *Race and Ethnicity.* There are few studies of measured GFR in populations other than Caucasians. In one study in India, the mean measured GFR determined using plasma clearance of Tc-DTPA (Diethethylene-triaminopenta-acetic acid) before and after amino acid infusion was 82.4 ± 12.7 ml/min/1.73 m^2. The difference compared to the available data in whites may be due to differences in protein intake. No studies of measured GFR have been performed in normal populations of blacks or other ethnic groups.
7. *Antihypertensive Therapy.* The level of GFR remains relatively constant throughout a wide-range of blood pressure. Nonetheless, antihypertensive therapy can be associated with reductions in GFR, due, in part, to the effect of lowering blood pressure and, in part, to specific effects of classes of antihypertensive agents. Indeed, marked reduction in GFR can complicate treatment in patients with severe hypertension and acute or chronic kidney disease,[17] an effect thought to be due to loss or reset of autoregulation due to sclerosis of the renal vasculature from hypertensive injury.[18] The effects of the individual antihypertensive agents are discussed in Chapter 12.

Measurement of Glomerular Filtration Rate

1. Physiology of Urinary Clearance and the Measurement of GFR

The "gold standard" for the measurement of GFR is the urinary clearance of an ideal filtration marker. The requirements for an ideal filtration marker are:[9]

a. It is freely filtered at the glomerulus. It passes from glomerular capillary blood into the Bowman space unhindered by its size, charge, or binding to plasma proteins.
b. It is not altered during its passage through the nephron. It is not reabsorbed, secreted, synthesized, or metabolized by the tubules.
c. It is physiologically inert. It does not alter the function of the kidney.

The clearance of a substance is defined as the rate at which it is cleared from the plasma per unit concentration. The clearance of substance "x" (Cx) is given by the following equation:

(Equation 3) $$Cx = Ax/Px$$

where Ax is the amount of x eliminated from the plasma and Px is the average plasma concentration.

Hence, Cx is expressed in units of volume per time and can be calculated without reference to the route of elimination.

For a substance that is cleared by urinary excretion, the clearance formula may be rewritten as follows:

(Equation 4) $$Cx = Ux \times V/Px$$

where Ux is the urinary concentration of x and V is the urine flow rate. The term Ux × V represents the urinary excretion rate of x.

If substance x is freely filtered at the glomerulus, then urinary excretion represents the net effects of glomerular filtration, tubular reabsorption, and secretion as follows:

(Equation 5) $$Ux \times V = GFR \times Px - TRx + TSx$$

where GFR × Px is the filtered load, and TRx and TSx are the rates of tubular reabsorption and secretion of x, respectively.

By rearrangement, GFR can be related to urinary clearance:

(Equation 6) $$GFR = (Ux \times V - TRx + TSx)/Px$$

(Equation 7) $$GFR = Cx - TRx/Px + TSx/Px$$

where TRx/Px and TSx/Px are the clearances of substance x due to reabsorption (CTRx) and secretion (CTSx), respectively.

If substance x is an ideal filtration marker, then GFR can be assessed from urinary clearance of x.

(Equation 8) $$GFR = Cx$$

2. True GFR versus Measured GFR

As described later, most filtration markers deviate from ideal behavior and clearance measurements are difficult to perform; thus, values for measured GFR often contain an element of error, which differentiates it from the physiological or "true GFR." True GFR, like other physiological properties, cannot be observed directly, but it can be modeled using the observed measured GFR and estimates of its error.

Measurement error is related to both the specific marker substance used and the clearance method and can be quantified in terms of bias and precision. Bias generally reflects systematic differences from the ideal filtration marker in renal handling, extrarenal metabolism, or assay of the filtration marker. Imprecision generally reflects random error in performance of the clearance procedure or assay of the filtration marker. Precision is assessed by repeated measurement over a short time and under standard conditions to minimize biological variation. Bias is assessed by comparison to an ideal filtration marker and standardized clearance method. Later, we will discuss clearance methods and filtration markers for assessment of GFR.

3. Clearance Methods
   a. *Urinary clearance.* Urinary clearance is the most direct method for measurement of GFR. Urine concentration of the filtration marker is assayed in a timed urine sample during which the plasma concentration is assayed. GFR is computed according to equation 4. This procedure is applicable for both exogenous and endogenous filtration markers.

      For an exogenous filtration marker, multiple (two to four) timed urine collections, each of approximately 20 to 30 minutes, are performed after administration of the marker, and the results are averaged. The classic method of Homer Smith includes fasting conditions in the morning, using a continuous intravenous infusion of the marker, multiple clearance periods requiring repetitive blood and urine collections over 3 hours, oral water loading to stimulate diuresis, bladder catheterization to ensure complete urine collection, and careful timing of blood sampling at the midpoint of the urine collection.

      As an alternative to continuous intravenous infusion, the exogenous filtration marker may be administered via bolus intravenous injection. This method requires additional blood samples to compute the average plasma concentration as it declines (see later). Subcutaneous bolus administration of the marker allows for slow release of the marker into the circulation, providing more constant plasma levels compared to intravenous bolus.[19] Spontaneous voiding is used in the majority of research studies and clinical practices.

      For an endogenous filtration marker, the urinary collection period may be prolonged to avoid the requirement for water loading, and a single plasma sample obtained either at the beginning or end of the collection period may be assumed to represent the average plasma concentration. A 24-hour urine collection is the method most commonly used in clinical practice, but it is subject to errors in timing and collection of the urine specimen.
   b. *Plasma clearance.* As an alternative to urinary clearance, GFR can be calculated from plasma clearance following a bolus intravenous injection of an exogenous filtration marker computed from equation 3, where Ax is the amount of the marker administered and Px is computed from the entire area under the disappearance curve or from 1-compartment or 2- compartment analysis of the slope of the plasma disappearance plot (Figure 2-2).

      Advantages of this method include the lack of requirement for urinary collection, which is particularly important in populations wherein bladder emptying may be impaired, such as the elderly or children with urinary tract abnormalities. In principle, plasma clearance methods would have greater precision than urinary clearance methods because they eliminate errors in timing of urine collection and incomplete bladder emptying. This has not been extensively tested.

      However, there are also several disadvantages to plasma clearance.[20] First, there is a relatively long time (~5 hours) required to determine the disappearance curve, with an even longer time required in people with very low GFR (8 to 10 hours). Shorter time periods may lead to overestimation of GFR throughout the GFR range. Second, a large volume of edema causes a prolongation of the first compartment of the two-compartment curve, and an overestimation of GFR. Third, extrarenal elimination of the filtration marker would lead to an overestimate of urinary clearance, which would be more apparent at lower GFR.

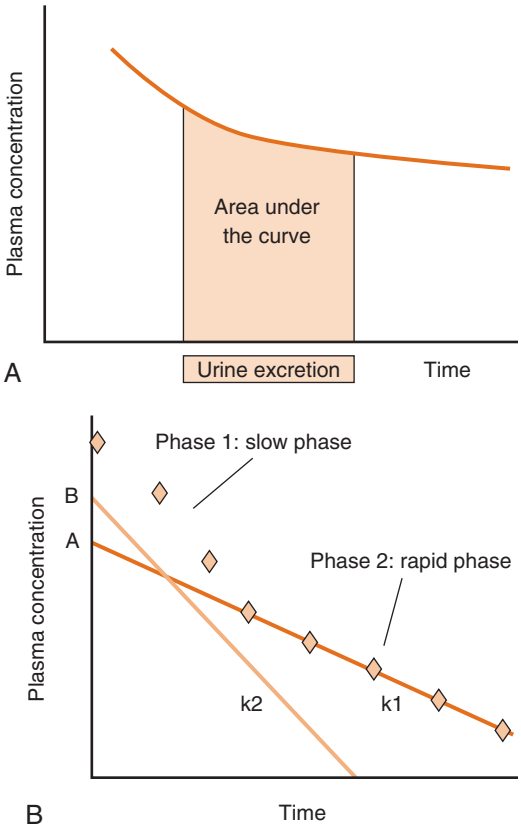


FIGURE 2-2 Plasma clearance.

   c. *Nuclear and other imaging.* Measurement of GFR by external counting or imaging over the kidneys and bladder using an exogenous isotopic marker substance is another alternative to urinary clearance.[21] Studies have been done in conjunction with dynamic kidney imaging using 99mTc-DTPA, comparing the percent kidney (and bladder) uptake at a defined time after injection to simultaneously measured GFR by other techniques. Several studies indicate low correlation of 99mTc-DTPA dynamic renal imaging with simultaneous urinary or plasma clearance, especially in people with normal and elevated GFR, reflecting both bias and imprecision.[10,22] It is premature to recommend external counting or imaging techniques for routine clinical purposes. The main value of dynamic renal imaging would appear to be in determining the function of each of the two kidneys or in for use in individuals already undergoing imaging procedures, rather than as a primary method of measuring GFR.

      Recently there has been consideration of magnetic resonance imaging (MRI) for measurement of GFR. Several techniques have been evaluated, including assessment of signal intensity within abdominal organs, measurement of the extraction fraction of the agent, and monitoring of tracer intrarenal kinetics.

None of these methods is regarded as optimal, and more study is required before MRI technology can be used for GFR measurement into clinical practice.[23,24]

4. Exogenous Filtration Markers

Inulin was used as the filtration marker in the classic studies by Homer Smith and remains the gold standard for endogenous filtration marker. There are now a wide variety of exogenous isotopic and nonisotopic filtration markers that are more available and simpler to use than inulin. The properties of inulin and these alternative filtration markers are described later (Table 2-1).

a. *Inulin.* Inulin, a 5200-dalton, inert, uncharged polymer of fructose, meets all the criteria for an ideal filtration marker.[10] It is administered as a continuous intravenous infusion with a long interval for equilibration throughout extracellular fluid because of its large molecular radius. However, inulin is difficult to dissolve in aqueous solutions, difficult to measure, and is in short supply. Because of these disadvantages, inulin is unsuitable for clinical assessment of GFR; other filtration markers are required.

b. *Iothalamate.* Iothalamate is commonly administered labeled with radioactive iodine for ease of assay, but can also be administered in its nonradioactive form and measured using high performance liquid chromatography (HPLC) methods. The filtration properties are not affected by the radiolabeling. ^{125}I-iothalamate, widely available in a pure, stable form (half life of ^{125}I is 60 days), is bound to protein to a minor degree.[10] Most, but not all, studies comparing urinary clearance of iothalamate to inulin show a small positive bias (overestimation of inulin clearance), likely due to tubular secretion of iothalamate.[10] Iothalamate is generally administered as a bolus subcutaneous injection in urinary clearance procedures, but can also be administered as bolus intravenous infusion or continuous subcutaneous infusion.[25]

c. *Iohexol.* Iohexol is a nonionic radiographic contrast agent that is administered using bolus intravenous injection and can be used for both urinary and plasma clearance. Recently, there has been much interest in iohexol as it provides several theoretical advantages over iothalamate.[20] It appears to exhibit neither protein binding nor tubular secretion, extrarenal elimination is minimal, it is stable in biological fluids, its adverse reactions are rare given the small dose (5 ml 300 mg/ml iodine when assayed with a sensitive assay, described later), and it does not require radioactive tags. Four small studies have compared plasma clearance of iohexol to urinary clearance of inulin. Two of these studies have shown a small underestimate of measured GFR, consistent with tubular reabsorption.[20]

The major disadvantage of iohexol is the complexity and expense of its assay. High-performance liquid chromatography, requiring a skilled technician and expensive equipment, must be used when low doses of iohexol (e.g., 5 ml of 300 mg/ml iodine) are administered. Other methods include x-ray fluorescence, but that necessitates administration of significantly larger doses of iohexol (10 to 90 ml of 300 mg/ml iodine) capillary electrophoresis, and neutron activation analysis.[20]

d. *Ethylene-diaminetetraacetic acid (EDTA).* There is an extensive European experience with 51Cr-EDTA in humans.[20] This marker is not commercially available in the United States. The urinary clearance of 51Cr-EDTA underestimates inulin clearance by 5% to 15% in most, though not all, studies, suggesting tubular reabsorption or protein binding.

e. *DTPA.* An analogue of EDTA, DTPA is usually labeled with 99mTc and is available in the United States. The advantages of 99mTc-DTPA include a short half-life (6 hours) that minimizes radiation exposure, the high counting efficiency of 99mTc, its availability on a daily basis in most nuclear medicine departments, and the convenience of using it to measure GFR at the time of renal imaging studies.[20] DTPA is freely filtered at the glomerulus, with minimal reabsorption by the tubules, but may undergo extrarenal elimination. One disadvantage is dissociation of 99mTc from the DTPA and protein binding of 99mTc, leading to underestimation of GFR. Rigorous quality control can minimize this error, and one recent study suggested that protein binding was similar to that of 51Cr- EDTA and ^{125}I-iothalamate. However, at least six different chelating kits and three technetium generators are in use in the United States, making standardization among institutions difficult.

The MRI contrast agent gadolinium (Gd)-DTPA has recently been discussed a novel exogenous filtration marker.[20] There is a highly sensitive novel immunoassay technique for serum and urine Gd. However, there is some concern about the risk of systemic nephrogenic fibrosis due to toxicity of Gd, even at the low levels administered for GFR measurement. The safety of Gd-DTPA and its accuracy and precision has not been thoroughly tested compared to other exogenous filtration markers.

ESTIMATION OF GLOMERULAR FILTRATION RATE

Clearance measurements are difficult to perform in clinical practice. Instead the level of GFR is usually estimated from the plasma or serum level of an endogenous filtration marker. In this section, we review the relationship of GFR to plasma solute concentrations, and then we focus on specific markers, including creatinine, urea, and cystatin C (Table 2-2).

Relationship of Glomerular Filtration Rate to Plasma Solute Concentrations

Determinants of Plasma Solute Concentrations

The plasma concentration of substance x reflects the balance of its rate of generation in body fluids (either from endogenous production or exogenous intake) and its rate of elimination from body fluids (either from excretion or metabolism) (Figure 2-3). In the steady state, the rate of generation and elimination from body fluids is equal and the plasma concentration of substance x is constant, thus the following equation applies.

(Equation 9) $$Gx = Ux \times V + Ex$$

where Gx is the rate of generation of x, and Ex is the extrarenal elimination of x.

TABLE 2-1 Properties of Exogenous Filtration Markers

MARKER TRACER	MOLECULAR WEIGHT (DALTONS)	PROTEIN BINDING	CLEARANCE METHODS		TUBULAR EFFECTS		EXTRARENAL ELIMINATION	ASSAY	SERIOUS ADVERSE SIDE EFFECTS
			ADMIN-ISTRATION	*URINARY*	*SECRETION*	*REABSORPTION*			
Inulin	5200	No	IV infusion	Urinary	None	None	None		None
Iothalamate									
^{125}I	614	Small	SC	Urinary	Small?	None	None	Gamma counter. T1/2 60 d	Oral KI required to protect the thyroid
Nonradioactive			IV/SC	Plasma* Urinary				HPLC	Anaphylatic reaction and contrast nephropathy at higher doses
Iohexol	821	No	IV/SC	Plasma* Urinary	None	Small	None	HPLC	Anaphylatic reaction and contrast nephropathy at higher doses
51Cr-Ethylene-diaminetetraacetic acid (EDTA)	292	Small	IV/SC	Plasma* Urinary	None	Small	None	Gamma counter T1/2 28d	
Diethylenetriamine pentaacetate (DTPA)									
99mTc	393	Yes	IV/SC	Plasma* Urinary	?	Small	None	Gamma counter T1/2 6 h	None
Gadolinium			IV/SC	Plasma* Urinary	?	?		RIA	Nephrogenic systemic fibrosis at low GFR

*Plasma clearances can only be calculated when marker is administered using intravenous route.

TABLE 2-2 Properties of Endogenous Filtration Markers

MARKER	MOL. WEIGHT (DALTONS)	MOL. DIAMETER (nm)	GENERATION	TUBULAR EFFECTS		EXTRARENAL ELIMINATION‡
				SECRETION	*REABSORPTION*	
Creatinine	116	0.3	Muscle, diet	++	None	Gut flora with advanced CKD
Urea	60	0.36	Liver, dietary protein, corticosteroids	+	+++	Not described
Cystatin C	13,347	3	Nucleated cells, corticosteroids, hyperthyroidism, smoking; ? Fat, inflammation, diabetes	None	Complete#	Not described

#, assumed; ‡, magnitude of effect.

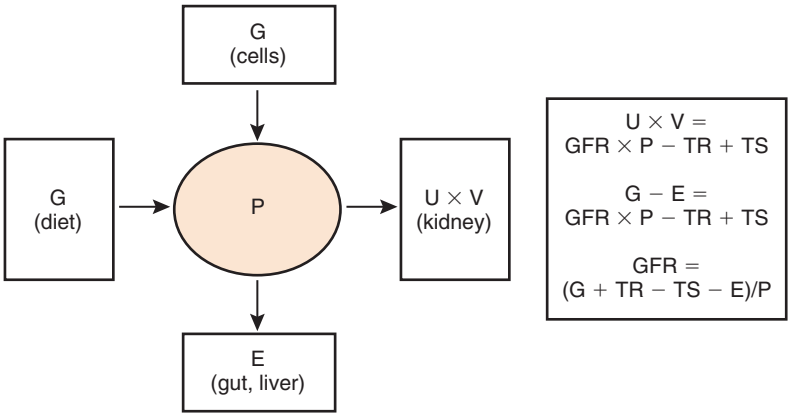


FIGURE 2-3 Determinants of the serum level of endogenous filtration markers. The plasma level (P) of an endogenous filtration marker is determined by its generation (G) from cells and diet, extrarenal elimination (E) by gut and liver, and urinary excretion (UV) by the kidney. Urinary excretion is the sum of filtered load (GFR × P), tubular secretion (TS) and reabsorption (TR). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, TR and E) to the plasma level. (From L.A. Stevens, A.S. Levey, Measured GFR as a confirmatory test for estimated GFR. J. Am. Soc. Nephrol. 20 [2009] 2305-2313.)

For substances excreted only in the urine (no extrarenal elimination), an important corollary is that, in the steady state, the rate of generation can be assessed from the urinary excretion rate.

By substitution of equation 9 and rearrangement, the plasma level can be related to the level of GFR and to its non-GFR determinants (Gx, TRx, TSx, and Ex).

(Equation 10) $$Px = (Gx + TRx - TSx - Ex)/GFR$$

Figure 2-4 shows hypothetical changes in generation, excretion, balance, and plasma level of substance x following a 50% decrement in GFR, assuming TR, TS, and E are zero. In the steady state, changes in the plasma level would reflect reciprocal changes in GFR. For example, a decline in GFR to two thirds, one half, or one third of the baseline level would be reflected by a rise in the plasma level to 1.5, 2.0, and 3.0 times the baseline level, respectively. Expression of the change in plasma level as its reciprocal (1/Px) would more clearly reflect the magnitude of changes over time in GFR in an individual.

Further rearrangement of equation 10 provides the conceptual framework for estimating GFR from plasma solute levels of endogenous filtration markers.

(Equation 11) $$GFR = (Gx + TRx - TSx - Ex)/Px$$

In practice, the non-GFR determinants of plasma solute levels are not measured. However, if the rates of these physiological processes were similar among all individuals and constant over time, then the level of GFR could be estimated directly from the inverse of the plasma concentration. Unfortunately, this is not the case for any of the currently used endogenous filtration markers.

Estimating Equations for Glomerular Filtration Rate

GFR estimating equations are equations that permit more accurate estimation of measured GFR from plasma levels of endogenous filtration markers and clinical and demographic variables than from the plasma level alone. GFR estimating equations are derived from regression analysis in which the level of measured GFR is related to the plasma solute concentration and observed clinical and demographic variables that serve as surrogates for the non-GFR determinants of plasma levels.

(Equation 12) $$GFR = (b \times X + c \times Y + d \times Z)/a \times Px + \varepsilon$$

where

X, Y, and Z = numerical values for clinical and demographic variables

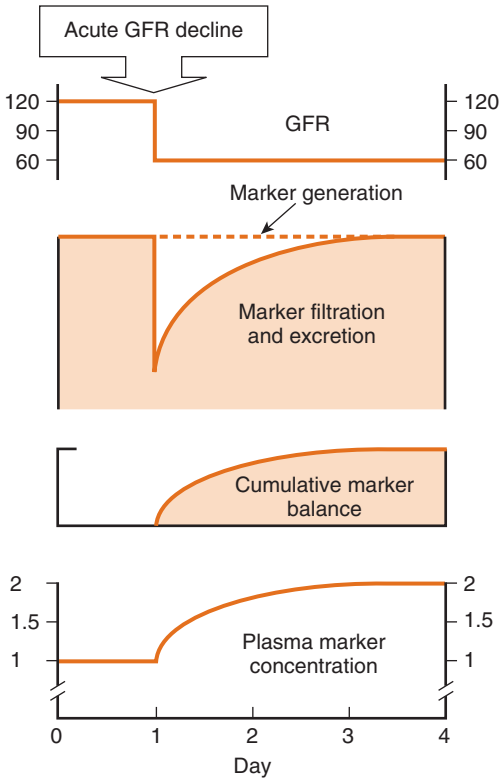
a, b, c, and d = coefficients relating Px and other variables to measured GFR

ϵ = the error based on uncertainty due to measurement, biological variability, and statistical techniques used to derive the coefficients

Estimating equations for GFR are often developed on the logarithmic scale, then exponentiated to report estimated GFR (eGFR) on the linear scale, and therefore have the appearance of:

(Equation 13) $$eGFR = (Px) - a \times Xb \times Yc \times Zd \times \varepsilon$$

where eGFR is estimated GFR, the negative sign for the coefficient a reflects the inverse relationship of plasma level of substance x to GFR. If the coefficient a is 1 and the



Day	P_{marker}	eGFR
1	1	120
1.5	1.6	79
2	1.8	69
2.5	1.9	65
3	2	60

FIGURE 2-4 Effect of an acute GFR decline on generation, filtration, excretion, balance, and serum level of endogenous filtration markers. After an acute GFR decline, generation of the marker is unchanged, but filtration and excretion are reduced, resulting in retention of the marker (a rising positive balance) and a rising plasma level (nonsteady state). During this time, estimated GFR (eGFR) is lower than measured GFR (mGFR). Although GFR remains reduced, the rise in plasma level leads to an increase in filtered load (the product of GFR times the plasma level) until filtration equals generation. At that time, cumulative balance and the plasma level plateau at a new steady state. In the new steady state, eGFR approximates mGFR. GFR expressed in units of ml/min/1.73 m^2. Tubular secretion and reabsorption and extrarenal elimination are assumed to be zero. (Modified and reproduced with permission from J.P. Kassirer, Clinical evaluation of kidney function-glomerular function, N. Engl. J. Med. 285 (1971) 385-389; Used with permission from L.A. Stevens, A. Levey, Measured GFR as a confirmatory test for estimated GFR. J. Am. Soc. Nephrol. 20 [2009] 2305-2313.)

variables b, c, and d are zero, then a rise in Px to 1.5, 2, and 3 times the baseline level would be reflected in a decline in eGFR to two thirds, one half, or one third of the baseline level, respectively.

Interpretation of Glomerular Filtration Rate Estimates

Development of accurate and generalizable estimating equations for widespread clinical use requires strict adherence to epidemiological and statistical principles.[26,27] In general, it is recommended that equations be developed in a large study population (>500 subjects), including a variety of racial and ethnic groups for international comparisons, using high-quality GFR measurements; validated to have adequate precision and low bias against a gold standard measure of GFR in an independent study population; and practical to implement, taking into consideration cost, required data elements, assay considerations, and generalizability.[28] Accuracy of GFR estimates in the validation population reflects bias, defined as average difference between the estimated and measured value for each subject, and precision, inversely related to the average variation of estimated values around the measured for each subject. Table 2-3 lists some of the metrics that can be used for the assessment of bias, precision, and accuracy, as well as the causes for bias and imprecision.[29] In general, knowledge of the sources of bias and imprecision can assist in interpretation of plasma levels of endogenous filtration markers and GFR estimates based on these levels. In this section, general principles are discussed; interpretation of GFR estimates from specific endogenous filtration markers are discussed separately later.

The coefficients for the clinical and demographic variables reflect average values for the relationship of the observed variables to the unmeasured surrogates in the development population.[30] Systematic differences in these relationships between the study and validation population is reflected as bias and generally reflects differences in selection between the study and validation populations. Random differences among individual patients are reflected as imprecision. In principle, use of multiple endogenous filtration markers with differing non-GFR determinants would cancel errors due to systematic bias in each filtration marker and improve precision.

There can be substantial variation among clinical laboratories in assays for endogenous filtration markers, leading to bias in GFR estimates between the study population in which the equation was developed and the population in which the equation is validated. This source of bias can be overcome by calibration of the clinical laboratory to the laboratory in which the equation was developed. In practice, this is best accomplished by standardization of clinical laboratories and reexpression of the GFR estimating equation for use with standardized values.

Measurement error in GFR in the study population is another source of inaccuracy in GFR estimates. This is a special case, however, because the difference is between measured and true GFR rather than between estimated and measured GFR. Systematic error in GFR measurement, due to the clearance method or the exogenous filtration marker, introduces a bias in GFR estimates compared to true GFR, which can lead to a bias in comparing GFR estimates to measured GFR in the validation population. Random error in GFR measurement leads to lower precision of GFR estimates compared to measured GFR than compared to true GFR in both the development and validation populations.

TABLE 2-3 Metrics for Evaluation of GFR Estimating Equations and Causes of Bias and Imprecision

CRITERIA	METRIC	DEFINITION	CAUSES*
Bias	Median difference	Measured GFR-Estimated GFR	Systematic difference between development and validation population in GFR measurement error (clearance method or exogenous filtration marker) Assays for endogenous filtration markers Non-GFR determinants of endogenous filtration marker (selection criteria) Mean level of measured GFR
	Median percent difference	(Measured GFR-Estimated GFR)/ Measured GFR	
Precision	SD difference	Standard deviation of the differences	Larger random variation in the validation than the development population True GFR (biological variation) GFR measurement error (clearance method or exogenous filtration marker) Non-GFR determinants of endogenous filtration markers
	IQR difference†	Interquartile range of (Measured GFR-Estimated GFR)	
	IQR % difference†	Interquartile range of ((Measured GFR-Estimated GFR)/Measured GFR)* 100	
Accuracy	Median absolute difference	Median of the absolute value of eGFR-mGFR	All of the above
	P30	Percent of estimates within 30% of measured GFR	
	RMSE	Square root of mean (log Measured GFR-log Estimated GFR)2	

Accuracy measures precision when bias is 0 (development dataset).
†IQR is the width of the 25th to 75th percentile.
*Differences between development and validation population.

A property of the statistical technique of regression is to "shrink" estimates to the mean of the study population in which they were developed. In the development population, the mean eGFR is unbiased, but higher values for measured GFR are systematically underestimated and lower values for measured GFR are systematically overestimated. In a validation population with a substantially different mean measured GFR, the estimates may be systematically biased due to "regression to the mean" of the development population. Because most GFR estimating equations are derived in a population with a wide range of GFR, this would lead to an underestimation of measured GFR in a validation population drawn from the general population, in which most subjects would be expected to have normal measured GFR.

All of these factors tend to cause larger errors in GFR estimation at higher values, in large part, because estimating equations are usually developed in study populations in which there are a large number of patients with reduced GFR and because development on the logarithmic scale leads to larger errors at the higher levels when estimates are reexpressed on the linear scale. Thus, eGFR is likely to be more accurate at lower values, as encountered in patients with kidney disease, and less accurate at higher values, as encountered in the general population.

Finally, it is difficult to estimate GFR in the nonsteady state (see Figure 2-4). This limitation applies both to plasma levels of endogenous filtration markers and to GFR estimates based on plasma levels. Nonetheless, a change in the plasma levels and eGFR based on plasma levels in the nonsteady state can be a useful indication of the magnitude and direction of the change in kidney function. If the plasma level is rising due to declining kidney function, then the decline in eGFR is less than the decline in measured GFR. Conversely, if the plasma level is falling due to rising kidney function, then the rise in eGFR is greater than the rise in measured GFR. The more rapid the change in the filtration marker or in eGFR, the larger the change in measured GFR. As kidney function stabilizes, the endogenous filtration marker reaches a new steady state, and eGFR more accurately reflects measured GFR.

CREATININE

Creatinine is the most commonly used endogenous filtration marker for estimation of GFR. Understanding basic concepts of metabolism, renal physiology, and analytical chemistry related to creatinine is essential to the interpretation of GFR estimates based on serum creatinine (Table 2-4).[31]

1. Structure and Function

Creatinine is a 113-dalton amino acid derivative that serves as a nitrogenous waste. It is distributed throughout total body water and has no known toxicity.

2. Plasma Levels

The normal level of GFR is sufficient to maintain a low concentration of creatinine in serum, approximately 0.64 to 1.36 mg/dl.

3. Generation

Creatinine is generated in muscle from the nonenzymatic conversion of creatine and phosphocreatine. Creatine is synthesized from arginine and glycine in the liver and actively concentrated in muscle. Thus, creatinine generation reflects the size of the creatine pool, which is proportional to muscle mass. In the steady state, creatinine generation can be estimated by creatinine excretion, and related to age, gender, and body size.[32]

TABLE 2-4 Clinical Conditions Affecting Interpretation of GFR Estimates

	CREATININE	UREA	CYSTATIN C*
Overestimation of GFR (Lower Serum Levels)			
Generation	Reduction in muscle mass; vegetarian diet	Severe malnutrition and liver disease	Lipids, hypothyroidism, female sex, older age
Renal handling	Proximal tubular injury; e.g., sickle cell disease		Not described
Extrarenal elimination	Increase with severe reduction in GFR	Not described	Spleen, diaphragm, heart, liver, and lungs
Assay			
Underestimation of GFR (Higher Serum Levels)			
Generation	Higher muscle mass and ingestion of cooked meats and creatinine supplements	Dietary protein intake, corticosteroids, diuretics, or tetracyclines; absorption of blood from the gut, infection, acute kidney injury, trauma, congestive heart failure, and sodium depletion	Steroid, inflammation hyperthyroidism, male, body mass index, transplant recipients
Renal handling	Decreased secretion with drugs such as cimetidine, trimethoprim, fibric acid derivatives other than gemfibrozil	Increase tubular reabsorption in presence of ADH	Not described
Extrarenal elimination	Decrease with antibiotic use	Not described	
Assay	Keto acids, some cephalosporins may interfere with alkaline picrate; flucytosine may interfere with enzymatic by as much as 60%	Ammonium in reagents or use of ammonium heparin; drugs such as chloral hydrate, chlorbutanol, and guanethidine	At high levels of bilirubin interference with the PETIA assay

*From population-based statistical analysis.

(Equation 14) $\text{Ucr} \times \text{V} = 28.2 - 0.172 \times \text{age (men)}$

(Equation 15) $\text{Ucr} \times \text{V} = 21.9 - 0.115 \times \text{age (women)}$

where creatinine excretion is expressed in mg/kg/d and age is expressed in years.

These equations do not take into account racial and ethnic differences in muscle mass. African American (black) males and females have higher muscle mass and consequently higher creatinine excretion than their Caucasian (white) counterparts. Asians have lower muscle mass and lower creatinine excretion.

Creatinine generation is also affected by diet and disorders of skeletal muscle. Muscle wasting is associated with a decreased creatine pool, leading to decreased creatinine generation and excretion. Reduction in dietary protein causes a decrease in the creatine pool by 5% to 15%, probably by reducing the availability of creatine precursors. Of greater importance is the effect of creatine in the diet. Creatine is contained largely in meat; elimination of creatine from the diet decreases urinary creatinine excretion by as much as 30%. Conversely, ingesting a creatine supplement increases the size of the creatine pool and increases creatinine excretion. Meat intake also affects creatinine generation and excretion independent of its effect on the creatine pool. During cooking, a variable amount of the creatine in meat is converted to creatinine, which is absorbed from the gastrointestinal tract. Following ingestion of cooked meat, there is a sudden transient increase in the serum creatinine concentration and urinary creatinine excretion.

4. Renal Handling

a. *Glomerular filtration.* The small molecular diameter of 0.3 nm and the lack of binding to plasma proteins assures the free passage of creatinine through the glomerular capillary wall into the Bowman space (sieving coefficient of 1).

b. *Tubular secretion.* Creatinine is actively secreted by the tubules, probably by the same pathway used for other organic cations in the proximal tubule; hence, creatinine clearance exceeds GFR.

(Equation 16) $\text{Ucr} \times \text{V} = \text{GFR} \times \text{Pcr} + \text{TScr}$

where TScr is the rate of tubular secretion.

The relationship between creatinine clearance and GFR is as follows:

(Equation 17) $\text{Ccr} = \text{GFR} + \text{TScr/Pcr}$

where TScr / Pcr represents creatinine clearance due to secretion (CTScr).

Using older assays for serum creatinine, which overestimate the level of serum creatinine in the low range, as described later, creatinine secretion in normal individuals was observed to account for 5% to 10% of excreted creatinine, on average, hence creatinine clearance exceeded GFR by approximately 10 ml/min/1.73 m^2. However, with the newer assays, creatinine clearance can exceed GFR by much larger amounts, suggesting higher rates of creatinine excretion.[33] Some studies find the levels of GFR, type of kidney disease, and the quantity of dietary protein intake to be determinants of creatinine secretion.[34] Several commonly used medications, including cimetidine and trimethoprim, competitively inhibit creatinine secretion, thereby reducing creatinine clearance and raising the serum creatinine concentration, despite having no effect on GFR. Clinically, it can be difficult to distinguish a rise in serum creatinine due to drug-induced inhibition of creatinine secretion from a decline in GFR. A clue to inhibition of creatinine secretion is that urea clearance and blood urea nitrogen concentration remain unchanged.

c. *Tubular reabsorption.* To a limited extent, creatinine may also be reabsorbed by the tubules, possibly due to its passive back-diffusion from the lumen to blood because of the high tubular creatinine concentration that occurs during low urine flow. Based on the clearance ratios observed in these studies, the maximum effect of creatinine reabsorption probably would be a 5% to 10% decrease in creatinine clearance.

d. *Extrarenal elimination.* Extrarenal loss of creatinine is not detectable in normal individuals, but may account for up to two-thirds of daily creatinine generation in patients with severe decrease in GFR. Thus, in patients with kidney disease, creatinine excretion underestimates creatinine generation:

(Equation 18) $$Ucr \times V = Gcr - Ecr$$

where Ecr is the rate of elimination of creatinine by extrarenal routes.

One likely, but still not established, mechanism is degradation of creatinine within the intestinal lumen by microorganisms due to induction of the enzyme "creatininase." Possibly, elimination of intestinal bacteria by broad-spectrum antibiotics could reduce extrarenal elimination of creatinine, thus causing a rise in serum creatinine without an effect on GFR. In practice, it would be difficult to distinguish a rise in serum creatinine due to drug-induced reduction in extrarenal creatinine elimination from a decline in GFR. As discussed previously for drug-induced reduction in creatinine secretion, a clue to inhibition of extrarenal elimination would be that urea clearance and blood urea nitrogen concentration remain unchanged.

5. *Assay* Creatinine can be measured easily in serum, plasma and urine by a variety of methods.[35] No systematic differences between serum and plasma have been noted. The gold standard method for creatinine assay is isotope dilution mass spectrometry (IDMS) using either gas or liquid chromatography. The National Kidney Disease Education Program (NKDEP) and the International Federation of Clinical Chemistry and Laboratory Medicine are currently standardizing serum creatinine assays to methods traceable to IDMS to minimize differences in across clinical laboratories. Standardization is expected to be complete in the United States in 2009.

   A variety of methods are in use in clinical laboratories to assay serum and urine creatinine. Calibration of autoanalyzers differs among clinical laboratories, irrespective of the method for measurement of serum creatinine. A survey by the College of American Pathologists in 2004 found the mean bias of the measured serum creatinine in 50 clinical laboratories compared to IDMS-traceable reference values varied from −0.06 to 0.31 mg/dl.[36] Variation in serum creatinine assays has important effects in clinical practice and in the interpretation of studies comparing GFR estimating equations based on serum creatinine.

   a. *Alkaline-picrate methods.* The classic method used the Jaffe reaction in which creatinine reacts directly with picrate ion under alkaline conditions to form a red-orange complex that is easily detected and quantified. In normal subjects up to 20% of the color reaction in serum or plasma is due to substances other than creatinine, resulting in an apparent creatinine value that is 20% higher than the true value. Noncreatinine chromogens are not present in sufficient concentration in urine to interfere with creatinine measurement. Hence, measured creatinine clearance using this assay was approximately 20% lower than the true value. As discussed previously, because of tubular secretion, the true creatinine clearance exceeds GFR. Therefore, the net result of these errors was that measured creatinine clearance deviated little from measured GFR in normal individuals. In patients with kidney disease, noncreatinine chromogens are not retained to the same degree as creatinine. Consequently, the overestimation of serum creatinine was reduced, as was the underestimation of creatinine clearance at lower GFR, and the discrepancy between measured GFR and measured creatinine clearance appears larger. As discussed hereafter, with the introduction of more accurate methods to measure serum creatinine, the discrepancy between creatinine clearance and GFR in normal individuals became apparent. To limit this discrepancy, some clinical laboratories calibrate the serum results to higher levels to maintain the relationship between creatinine clearance and GFR. With standardization of serum creatinine assays to more accurate methods, clinical laboratories will no longer be expected to "adjust" their creatinine values, and therefore the discrepancy will be unmasked.

      The kinetic alkaline-picrate method takes advantage of the differential rate of color development for noncreatinine chromogens compared to creatinine. It significantly reduces, but does not eliminate the positive interferences described previously. Many laboratories using these methods continue to calibrate their creatinine to minimize the discrepancy between creatinine clearance and measured GFR.

   b. *Enzymatic methods.* To circumvent interferences in the alkaline picrate reaction, a variety of enzymatic methods have been developed. Two are in use in clinical laboratories: the creatinine iminohydrolase method; and the creatininase, creatinase, and sarcosine oxidase method. Both methods have been reported to have fewer interferences than the alkaline-picrate methods.

   c. *HPLC.* HPLC is a fairly sensitive and analytically specific method for measuring serum creatinine. Many of these protocols have included deproteinization to obviate the effects from interfering compounds.

      All of the commonly used methods are imprecise in the lower range of serum creatinine. The imprecision makes it difficult to interpret changes in serum creatinine within the normal range, as one cannot readily distinguish between differences in serum creatinine levels due to errors in the assay or due to biological variability in GFR.

6. *Creatinine as a filtration marker* Based on the previous considerations, the relationship of GFR to serum creatinine is expressed as follows.

(Equation 19) $$GFR = (Gcr - TScr - Ecr)/Pcr$$

The use of serum creatinine as an index of GFR rests on the assumption that generation, tubular secretion, and extrarenal elimination of creatinine are similar among

individuals and constant over time. As described previously, none of these assumptions is strictly correct, and it is difficult to estimate the level of GFR from serum creatinine alone (see Table 2-4). The rate of creatinine generation is lower in people with reduced muscle mass (women, children, the elderly, and malnourished individuals) and those with restricted meat intake.

Estimating equations overcome some of these limitations of using serum creatinine alone to estimate GFR by incorporating known demographic and clinical variables as observed surrogates for creatinine generation. Over the years, a large number of equations have been developed to estimate creatinine clearance and GFR in adults.[37] However, only the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations have been reexpressed for use with standardized creatinine.

One of the most common estimating equations used to estimate creatinine clearance is the Cockcroft-Gault formula, due to its relative ease of use.[38]

(Equation 20)

$$\text{eCcr} = \frac{(140 - \text{Age} \times \text{body weight}) \times 0.85 \text{ (if female)}}{(\text{Scr} \times 72)}$$

where eCcr is estimated creatinine clearance in ml/min, Scr is expressed in mg/dl, age is expressed in years, and body weight is expressed in kg.

The formula for men was derived from measurements of serum creatinine and urinary creatinine excretion. The formula for women was based on the assumption that creatinine generation is 15% less in women than in men. The Cockcroft-Gault formula was derived in Caucasians; hence, it may underestimate creatinine clearance in African Americans. One recent study compared the Cockcroft-Gault equation to measured GFR in a large, diverse population developed from a pooled database (Figure 2-5B).[39] Using nonstandardized creatinine values, the Cockcroft-Gault equation showed only a 1.1 ml/min/1.73 m^2 overestimation of measured GFR, consistent with previously described cancellation of biases due to the effects of noncreatinine chromogens in older assays and creatinine secretion. With standardized creatinine values, the overestimation of measured GFR rose to 5.5 ml/min/1.73 m^2. In comparison the improvement with standardized values are shown in Figure 2-5A.

At present, the most commonly used equations to estimate GFR are the four-variable MDRD Study equations using nonstandardized or standardized creatinine.[40–42]

(Equation 21)

$$\text{eGFR} = 186 \times \text{non-standardized Scr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

(Equation 22)

$$\text{eGFR} = 175 \times \text{standardized Scr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

where eGFR is expressed in ml/min/1.73 m^2, Scr is expressed in mg/dl, and age is expressed in years.

The MDRD Study equation was developed in a study population of 1628 patients with chronic kidney disease (mean GFR 40 ml/min/1.73 m^2) who were predominantly Caucasian and had predominantly nondiabetic kidney disease. GFR was measured using urinary clearance of ^{125}I-iothalamate and serum creatinine was measured using a kinetic alkaline-picrate assay. As shown by the Scr coefficient of less than −1, the relationship of eGFR to Scr is more steep than in the hypothetical relationship in which there are no non-GFR determinants of the filtration markers. A rise in the plasma level to 1.5, 2,

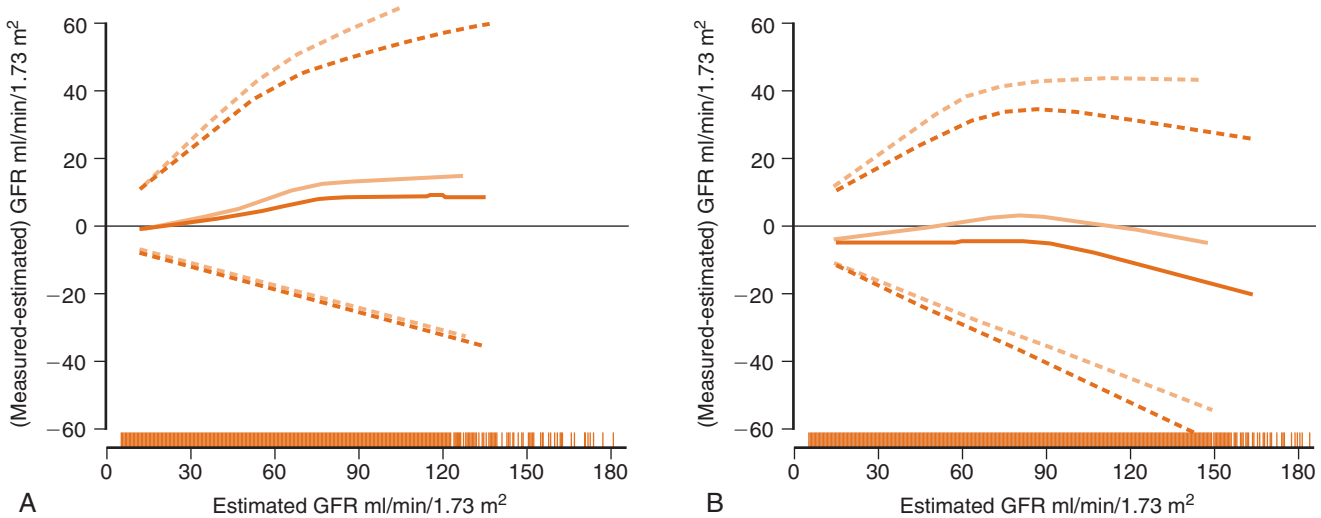


FIGURE 2-5 Performance of the MDRD Study and Cockcroft-Gault equation before and after calibration of serum creatinine assays by level of eGFR. Shown are lowess smooth line(*solid curve*) and 95% CI using quantile regression (*dashed lines*) for the CKD-EPI development dataset, excluding lowest and highest 2.5% of estimated GFR values. Black line is for calibrated serum creatinine and gray line is for noncalibrated serum creatinine. For the MDRD Study equation **(A),** calibration led to improved performance with a decrease in median difference (IQR) from 4.3 (18.6) to 2.7 (16.4), and P30 went from 80 to 83%. For the Cockcroft-Gault equation **(B),** calibration worsened median difference (IQR) from x−1.1(19.6) to −5.5 (18.6), and the P30 from 74% to 69%. (Used with permission from L.A. Stevens, J. Manzi, A.S. Levey, et al., Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database, Am. J. Kidney Dis. 50 [2007] 21-35.)

and 3 times the baseline value, is associated with a decline in eGFR to 73%, 45%, or 28% of the baseline value, respectively, if all other factors are constant. The MDRD Study equation is more accurate than the Cockcroft-Gault equation (see Figure 2-5). The MDRD Study equation has been validated in African Americans with hypertensive nephrosclerosis, diabetic kidney disease, and kidney transplant recipients.[43–46] It is unbiased in individuals with eGFR less than 60 ml/min/1.73 m^2, but it underestimates measured GFR at higher levels of eGFR, and it is relatively imprecise.

Recently, a new estimating equation, the CKD-EPI equation, has been developed that overcomes some of the limitations of the MDRD Study equation.[47]

(Equation 23)

$$\text{eGFR} = 141 \times \min(\text{Scr}/\kappa, 1)\alpha \times \max(\text{Scr}/\kappa, 1)1.209 \times 0.993\text{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$$

where eGFR is expressed in ml/min/1.73 m^2, Scr is standardized serum creatinine expressed in mg/dl age is expressed in years, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr/κ or 1.

The CKD-EPI equation was developed in a study population of 5504 individuals, derived from 10 studies, with a mean GFR of 68 ml/min/1.73 m^2 and a wide range of age, and included both men and women, whites and blacks, and subjects with and without kidney disease, diabetes, and kidney transplants.

GFR was measured as urinary clearance of ^{125}I-iothalamate. The equation was validated in a separate population of 3859 individuals from 16 studies. The CKD-EPI equation is based on the same variables as the MDRD Study equation; additional terms to characterize individuals according to presence or absence of diabetes, history of organ transplantation, or weight did not improve accuracy. The CKD-EPI equation differs from the MDRD Study equation principally by having a two-slope relationship between eGFR and Scr and a steeper relationship between eGFR and age. Figure 2-6 compares the performance of the CKD-EPI and MDRD Study equations in the validation population. The CKD-EPI equation has a lower bias than the MDRD Study equation, especially at higher GFR. Precision is improved, but it is still suboptimal. As with the MDRD Study equation, the CKD-EPI equation does not include terms for racial or ethnic groups other than blacks or whites.

There are limitations to the use of all estimating equations based on serum creatinine. Age, sex, and race serve as surrogates of creatinine generation, but do not account for differences in creatinine generation due to effects of diet, nutritional status, and chronic illness on muscle mass. This is especially important in acute and chronic kidney diseases that may lead to reduced creatinine generation due to reduction in protein intake (especially meat), malnutrition, and muscle wasting, and may enhance creatinine secretion and extrarenal elimination. These factors tend to blunt the rise in serum creatinine as GFR declines, and they may cause serious overestimation of the level of GFR from serum creatinine.

Even among patients without kidney disease, differences in race and ethnicity are likely to be confounded with differences in creatinine generation, thus requiring development and validation of multiple terms for use throughout the world.[48] Malnutrition and chronic illness are likely to be more common in the elderly. Accurate GFR estimates are especially important in the elderly due to the high prevalence of chronic kidney disease. It is not likely that variation in other non-GFR determinants of serum creatinine, such as drug-induced inhibition of secretion or extrarenal elimination, will be captured by routinely-used equations. Standardized assays will overcome limitations due to variation in creatinine calibration, but even standardized assays are less precise at low values; therefore, errors in GFR estimates may be greater in normal adults, in whom serum creatinine is low because of normal GFR, and in children, in whom serum creatinine is low because of lower muscle mass. Table 2-4 lists clinical situations in which estimating equations for creatinine clearance or GFR may not be accurate and clearance measurements may be indicated.

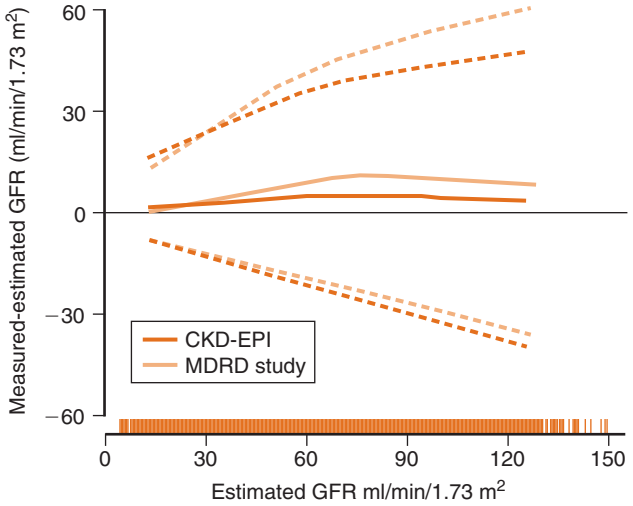


FIGURE 2-6 Comparison of performance of MDRD Study and CKD-EPI equations by estimated GFR shown are lowess smooth line (*solid curve*) and 95% CI using quantile regression (*dashed lines*), for the CKD-EPI validation dataset excluding lowest and highest 2.5% of estimated GFR values. The CKD-EPI equation is in black and the MDRD Study equation is in gray. The CKD-EPI equation has improved performance compared to the MDRD Study equation with a decrease in median difference (IQR) from 2.7 (14.7) to 0.4 (16.4), and P30 went from 83% to 86%.

UREA

A relationship between plasma urea and kidney function was recognized long before the development of the concept of clearance or of techniques to assess GFR.[49] The factors influencing both the generation of urea and its excretion by the kidney are considerably more complex and variable than those for creatinine (see Table 2-4).[50] As a result, serum urea nitrogen concentration (SUN, for historical reasons, often referred to as the blood urea nitrogen or BUN) has been replaced largely by the serum creatinine as a filtration marker in routine clinical practice. Nonetheless, measurement of the SUN remains useful both as a diagnostic aid in distinguishing among the various causes of acute decline in GFR and as a rough correlate of uremic symptoms in kidney failure. A brief summary of the properties of urea is presented hereafter.

1. Structure and Function

Urea is a 180-dalton molecular weight compound derived from deamination of amino acids. It is a nitrogenous waste product, accounting for more than 75% of nonprotein nitrogen excreted by the body. Urea is freely distributed in total body water. At high levels (greater than 100 mg/dl), urea has neurotoxicity.

2. Plasma Levels

Plasma urea is affected by numerous factors in addition to GFR, thus its plasma levels in normal individuals vary over a wider range than creatinine, from approximately 15 to 45 mg/dl.

3. Generation

The metabolism of urea, its relationship to dietary protein intake, and the effect of kidney disease on protein metabolism are discussed in detail in Chapter 12. Briefly, urea is the product of protein catabolism and is synthesized primarily by the liver. Approximately one quarter of synthesized urea is metabolized in the intestine to carbon dioxide and ammonia, and the ammonia thus generated returns to the liver and is reconverted to urea.

Dietary protein intake is the principal determinant of urea generation and may be estimated as follows:

(Equation 24) $$EPI = 6.25 \times GUN$$

where EPI is estimated protein intake, GUN is urea generation, and both are measured in g/d.[50]

Usual protein intake in the United States is approximately 100 g/d, corresponding to a usual value for urea nitrogen generation of approximately 15 g/d.

In the steady state, urea generation can be estimated from measurements of urea excretion, as shown below:

(Equation 25) $$GUN = UUN \times V + 0.031 \times \text{weight}$$

where GUN and UUN × V are measured in g/d, weight is measured in kg, and 0.031 g/kg/d is a predicted value for nitrogen losses other than urine urea nitrogen.[51]

For a 70-kg individual with a dietary protein intake of 100 g/d, urea excretion and other nitrogen losses would be approximately 13 g/d and 2 g/d, respectively.

Urea generation is also influenced by factors other than protein intake (see Table 2-4). An increase is observed after administration of corticosteroids, diuretics, or tetracyclines; after absorption of blood from the gut; and in infection, acute kidney injury, trauma, congestive heart failure, and sodium depletion. Decreases in urea generation may occur in severe malnutrition and liver disease.

4. Renal Handling of Urea

Urea (molecular diameter 0.36 nm) is uncharged, not bound to plasma proteins, and freely filtered by the glomerulus and reabsorbed in both the proximal and distal nephron. Hence urea excretion (UUN × V) is determined by both the filtered load and tubular reabsorption (TRUN)

(Equation 26) $$UUN \times V = GFR \times SUN - TRUN$$

where TRUN is tubular reabsorption of urea.

Consequently, clearance of urea (or urea nitrogen, CUN) is less than GFR:

(Equation 27) $$CUN = GFR - TRUN/SUN$$

where TRUN / SUN is clearance of UN by tubular reabsorption (a negative quantity).

In the proximal convoluted tubule, a large fraction of the filtered load of urea is reabsorbed regardless of the state of diuresis. In the medullary collecting duct, urea reabsorption is closely linked to water reabsorption. In the absence of antidiuretic hormone (diuresis), the medullary collecting duct is relatively impermeable to urea; thus, urea reabsorption is minimal. Conversely, in the presence of antidiuretic hormone (antidiuresis), permeability rises and urea reabsorption increases. In normal individuals, the ratio of urea clearance to GFR varies from as high as 0.65 during diuresis to as low as 0.35 during antidiuresis.

In patients with GFR less than 20 ml/min/1.73 m^2, the ratio of urea clearance to GFR is higher (0.7 to 0.9) and is not influenced greatly by the state of diuresis. Thus urea clearance is approximately 5 ml/min less than GFR. By coincidence, at this level of GFR, the difference between the values of GFR and urea clearance is similar to the difference between the values of creatinine clearance and GFR, providing a relatively simple method to assess GFR in severe kidney disease.[52,53]

(Equation 28) $$GFR = (Ccr + CUN)/2$$

However, the kidney handling of urea and creatinine are influenced by different physiological and pathological processes and may vary independently, causing deviations from this approximation.

5. Extrarenal Elimination

More than 90% of urea is excreted by the kidneys, with losses through the gastrointestinal tract and skin accounting for most of the remaining fraction.

6. Assay

The urease method assays the release of ammonia in serum or urine after reaction with the enzyme urease.[54] A variety of systems for detection of ammonium are available, all with good precision and specificity. The presence of ammonium in reagents or use of ammonium heparin as an anticoagulant may falsely elevate the SUN. Urea is also subject to degradation by bacterial urease. Bacterial growth in urine samples can be inhibited by refrigerating the sample until measurement or by adding an acid to the collection container to maintain urine pH below 4.0.

7. Urea as a Filtration Marker

In the steady state, the SUN level reflects the levels of urea clearance and generation.

(Equation 29) $$GFR = (GUN + TRUN)/SUN$$

Consequently, many factors influence the level of SUN (see Table 2-4). Nonetheless, the SUN can be a useful tool in some clinical circumstances.

As mentioned earlier, the state of diuresis has a large effect on urea reabsorption and a small effect on GFR, but it does not affect creatinine secretion. Hence, the state of diuresis affects urea clearance more than creatinine clearance and is reflected in the ratio of SUN to Scr. The normal ratio of SUN to Scr is approximately 10:1. In principle, a reduction in GFR without a change in the state of diuresis would not alter the ratio. However, conditions causing antidiuresis (dehydration or reduced renal perfusion) would decrease GFR and increase urea reabsorption, thus raising the SUN-to-Scr ratio. Consequently, the SUN-to-Scr ratio is may be useful aid in the differential diagnosis of acute kidney injury. Conversely, overhydration or increased renal perfusion would raise GFR and decrease urea reabsorption, thus lowering the serum creatinine and the SUN-to-Scr ratio. However, conditions affecting urea generation may also affect the SUN and the SUN-to-Scr ratio when GFR is decreased, limiting the use of this ratio as a guide to the status of hydration and kidney perfusion in patients with Acute Kidney Injury (AKI).

Also important is the well-recognized relationship of the level of kidney function, the SUN level, and clinical features of uremia. A traditionally used rule to thumb is that a SUN level greater than 100 mg/dl is associated with a higher risk of complications in both acute and chronic kidney failure and may indicate the need to initiate dialysis, although SUN may exceed this level without apparent clinical effects in many clinical circumstances.[55–57] The role of high concentrations of urea versus other retained nitrogenous wastes in causing symptoms of uremia is not well known, despite decades of investigation. In both acute and chronic kidney disease, restriction of dietary protein intake to 40 to 50 g/d would reduce urea nitrogen excretion to approximately 4.5 g/d. Consequently, the SUN level might rise to only 40 to 60 mg/dl, despite severe reduction in GFR. Although protein restriction may temporarily ameliorate some of the uremic symptoms, severe reduction in GFR is associated with development of uremic symptoms, despite only moderate elevation in SUN.

CYSTATIN C

Cystatin C has been proposed as an endogenous filtration marker to be used as an alternative or in addition to creatinine due in part to its better prediction of adverse events.[58] A summary of issues related to its structure, generation, renal handling, metabolism, measurement, and use as an index of GFR is presented below.

Structure and Function

Cystatin C is a 3343-dalton protein consisting of 120 amino acid residues in a single polypeptide chain.[59] Cystatin C regulates the activities of cysteine proteases to prevent uncontrolled proteolysis and tissue damage.[60,61]

Plasma Levels

The reference range for serum cystatin C is listed as 0.52 to 0.98 mg/l. However, the true "normal level" is not well known. Several epidemiological studies have examined causes for variation in cystatin C levels.[62–65] In a sample of noninstitutionalized U.S. population, the third National Health and Nutrition Examination Survey (NHANES III), the median plasma cystatin C level was 0.85 mg/l, with 1.12 mg/l as the upper 99th percentile for young people 20 to 39 years of age who did not have hypertension and diabetes.[66] The level of cystatin C was related to age, sex, and ethnicity, with the median serum level estimated at 8% lower in women than men, and it increased steeply with age and was greater in non-Hispanic whites (Figure 2-7). Prevalence of increased serum cystatin C levels (>1.12 mg/l) were 1%, 41%, and greater than 50% in people younger than 20 years, 60 years and older, and 80 years and older respectively. In a multivariable analysis, older age, non-Hispanic white ethnicity, hypertension, current smoking, lower levels of education, lower high-density lipoprotein, and higher body mass index, C-reactive protein. and triglyceride values are associated with increased serum cystatin C levels.[66]

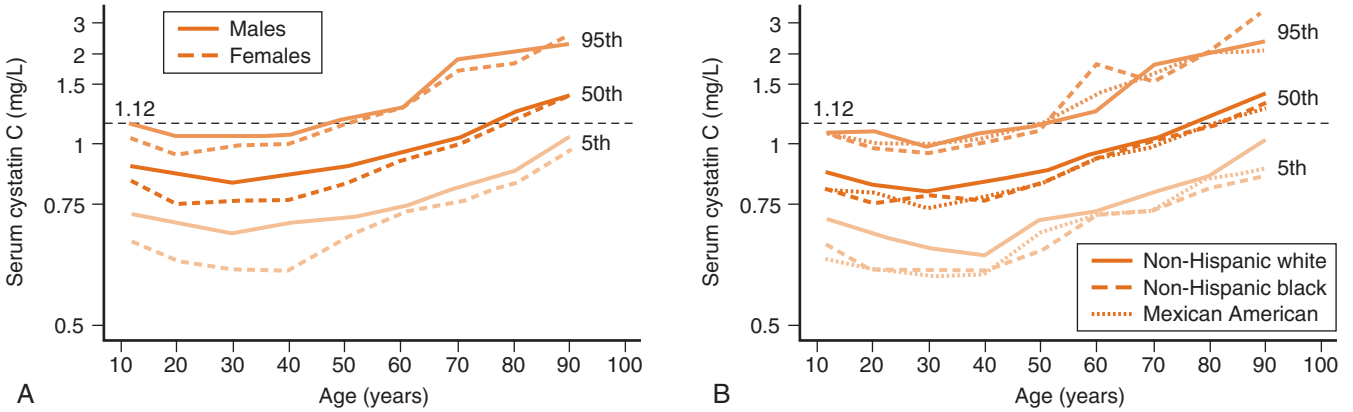


FIGURE 2-7 Serum levels of cystatin C in the United States by age, sex, race, and ethnicity. Serum cystatin C percentiles (5th, 50th, and 95th) by age and **(A)** sex and **(B)** race/ethnicity graphed by using an inverse transformation. (-1/cystatin C) is analyzed and the corresponding values for serum cystatin C are shown on the *y*-axis. The horizontal line at a serum cystatin C value of 1.12 mg/L indicates the cutoff value for increased serum cystatin C level. (Used with permission from A. Kottgen, E. Selvin, L.A. Stevens, et al., Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III), Am. J. Kidney Dis. 51 [2008] 385-394.)

Generation

Cystatin C is thought to be produced by all human nucleated cells at a stable rate.[60,61] As described later, cystatin C is not excreted in the urine; therefore, studies of its generation have used in vitro or statistical approaches. However, indirect evidence suggests that under certain conditions, there is variability in the generation rate, in particular with states associated with higher or lower cell turnover. For example, serum cystatin C levels are significantly increased in overt hyperthyroid patients and significantly decreased in hypothyroidism. In a prospective study, restoration of euthyroidism by either methimazole or L-thyroxin therapy was associated with normalization of the cystatin C concentrations.[67] In vitro treatment of mouse peritoneal macrophages with either lipopolysaccharides or interferon-gamma caused a downregulation in cystatin C secretion.[68] Conversely, transforming growth factor β increases cystatin C expression in mouse embryo cells.[69] In vitro experiments using dexamethasone in HeLa cells showed a dose-dependent increase in cystatin C production[70] and clinical studies suggest glucocorticosteroids are associated with higher cystatin C levels. In one study, children who were transplant recipients taking prednisone had higher levels of cystatin C than children not on prednisone.[71] In another study, cystatin C level was reported 19% higher in transplant recipients than in patients with native kidney disease,[72] possibly due to the use of corticosteroids.

Two studies have attempted to examine the non-GFR determinants by examining the significant predictors of cystatin C after adjustment for creatinine clearance or measured GFR. A population-based study in Groningen, the Netherlands showed that even after adjusting for the level of creatinine clearance, older age, male sex, higher body mass index, and higher C-reactive protein were significantly related to higher levels of cystatin C.[73] In a second study of 3418 patients with CKD, after adjustment for measured GFR, higher levels of cystatin C were associated with male sex, white race, diabetes, higher C-reactive protein and white blood cells, and lower serum albumin,[74] and in contrast to the first study, this study showed that older age was associated with lower levels of cystatin C after adjustment for GFR.

Renal Handling

Cystatin C is thought to be completely filtered at the glomerulus, taken up by the proximal tubular cells and then catabolized, such that no cystatin C is found in the urine under normal conditions.

a. *Glomerular filtration.* The molecular diameter of cystatin C (3 nm) suggests that it can be freely filtered by the glomerulus. The clearance of purified recombinant human ^{125}I-labelled cystatin C was compared with clearance of 51Cr-EDTA in rats, and was observed to be 94% of 51Cr-EDTA clearance (GFR).[75] When the GFR of the rats was lowered by constricting their aortas above the renal arteries, the clearance of cystatin C correlated strongly with that of 51Cr-EDTA with a correlation coefficient of 0.99.[75]

b. *Tubular reabsorption.* In this same study, free ^{125}I was observed in the plasma after 20 minutes. This was interpreted as evidence for reabsorption of cystatin C into the proximal tubules, with subsequent degradation and release of free ^{125}I release into the plasma. Urine ^{125}I accounted for 0.2% of the total ^{125}I activity detected in the kidney and the urine, indicating near complete tubular uptake of filtered ^{125}I cystatin C. Immunohistochemical and Northern blot studies of human kidneys indicate that human cystatin C is degraded by proximal tubular cells after its passage through the glomerular membrane.[76] In another study, the amount of ^{125}I labeled cystatin C uptake in the rat kidney fell exponentially along the proximal convoluted tubule, indicating a cystatin C uptake proportional to luminal concentration.[77] There is increasing evidence that the presence of cystatin C in the urine is due to failure of reabsorption due to tubular damage.[78,79]

c. *Tubular secretion.* Renal tubular secretion of cystatin C was indirectly evaluated by comparison of its renal extraction to that of ^{125}I-iothalamate in hypertensive patients,[80] with the results not suggesting any evidence of tubular secretion.[81]

d. *Extrarenal elimination.* Extrarenal elimination of cystatin C was observed to occur in the spleen, diaphragm, heart, liver, and lungs in nephrectomized rats and was estimated at approximately 15% of the total cystatin C elimination.[75,82]

e. *Assay.* There are two primary methods by which commercially available autoanalyzers assay cystatin C: particle-enhanced turbidimetric immunoassay (PETIA)[83] or particle-enhanced nephelometric immunoassay (PENIA).[84] Although when similarly calibrated, results from these two different methods are highly correlated,[65] other studies demonstrate considerable variation (up to 50%) using these different methods.[85] With the PENIA method, no interference is noted with common interfering factors such as bilirubin, rheumatoid factor, hemoglobin, or triglycerides. The PETIA method also shows minimal interference with these substances, but bilirubin levels of 150 to 300 μmol/liter (8.8 to 17.5 mg/dl) raise cystatin C levels by less than 10%.[83]

An International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Standardization of Cystatin C has recently been established. Its goals are to produce and characterize both a primary and a secondary reference preparation for cystatin C. The primary reference preparation is a recombinant human cystatin C produced by expression in *Escherichia coli*. The Secondary Reference Preparation is expected to be released soon, when the commercial calibrators can be adjusted accordingly.[86]

f. *Cystatin C as an index of kidney function.* Studies have compared serum cystatin and creatinine as filtration makers. There is a better correlation of serum cystatin C with GFR than serum creatinine levels alone,[64,65,83,87–89] thus providing an alternative GFR estimate that is not linked to muscle mass. However, GFR estimates based on serum cystatin C alone are comparable or slightly less accurate than estimates based on serum creatinine, such as those computed from the MDRD Study equation. An estimating equation including both serum cystatin C and creatinine, with age, sex, and race was developed in 1935 patients with CKD and mean GFR of 51 ml/min/1.73 m^2 was shown to provide the most accurate estimates.[90]

It is likely that the advantage of cystatin C over creatinine as a filtration marker would be most apparent in populations that are most susceptible to the limitations of serum creatinine and its association with muscle mass.

a. *Elderly.* Some studies,[91,92] but not all,[93,94] indicate that cystatin C is a more sensitive marker for detecting early CKD in the elderly than serum creatinine while other studies failed to show the difference. In the population with CKD described previously, cystatin-based estimating equations were not better than creatinine alone, even in those older than 65 years of age.[90]
b. *Transplant patients.* Some studies showed significantly better performances of cystatin C–based GFR-estimating equations compared to the MDRD study equation in adult transplant recipients,[81,95,96] whereas other studies did not reveal any superiority of cystatin C in stable renal transplant patients.[97]
c. *Chronic illness.* Several studies suggest that cystatin C is a better estimate of GFR than creatinine in patients with cirrhosis,[98,99] cystic fibrosis,[100,101] and cancer.[102] However, in one study of patients with cirrhosis, both creatinine and cystatin C provided estimates that were 100% greater than the measured GFR.[103]
d. *Children studies.* Studies do not show any significant advantage of cystatin C over creatinine in children.[104–105] Similar to adults with CKD, an equation with serum creatinine, cystatin C, and SUN in 349 children with CKD showed better performance than equations with any marker alone.[106] In one study of children with cancer, cystatin C provided more accurate estimates than serum creatinine.[107]
e. *Acute kidney injury.* In acute GFR decline, studies in animals[108] and in humans[109,110] demonstrate that cystatin C increases prior to serum creatinine and has been interpreted as a more sensitive marker. Comparisons to changes in measured GFR have not been performed.

Overall, most studies in these special populations are small and have not used calibrated serum creatinine in the MDRD Study equation, precluding definitive conclusions. Prior to the potential widespread adoption of serum cystatin C levels for the estimation of GFR, more research is required.

NOVEL ENDOGENOUS MARKERS

There are several alternative novel endogenous under investigation as potential markers that could replace or be used in combination with creatinine, urea, or cystatin. For optimal clinical use, it is important to first understand their non-GFR determinants and factors associated with deviations in these determinants, as discussed previously. In principle, use of multiple endogenous filtration markers with differing non-GFR determinants would cancel errors due to systematic bias in each filtration marker and improve precision. Another important consideration for the introduction of novel filtration markers is the availability of an assay that can be easily implemented and standardized across all clinical laboratories.

It is beyond the scope of this chapter to discuss novel markers in detail. Two promising candidate markers include beta trace protein[111–127] and beta-2-microglobulin. Symmetrical dimethyl-arginine has also been studied but appears to have lower correlation than creatinine in most studies.[128–130]

A full list of references are available at www.expertconsult.com.

Chapter 3

DIABETIC KIDNEY DISEASE: CURRENT CHALLENGES

Mark E. Williams, M.D., F.A.C.P, F.A.S.N.
and Robert C. Stanton, M.D.

The prevalence of both diabetes mellitus and chronic kidney disease (CKD) continues to increase in the United States, constituting an impending public health crisis.[1] According to the annual health report from the U.S. Deptartment of Health and Human Services, the epidemic of diabetes mellitus in the United States continues to get worse. The percentage of Americans diagnosed with diabetes increased 27% between the years 1997 and 2000, and the percentage of Americans diagnosed with diabetes in 2002 rose to 6.5%, up from 5.1% in 1997.[2] The Centers for Disease Control and Prevention estimates that in addition to 18 million Americans diagnosed with diabetes, up to 6 million others have it but have not been diagnosed. The number of Americans diagnosed with diabetes mellitus has increased 61% over the last decade and will more than double by the year 2010.

Diabetic nephropathy is a potentially devastating complication of diabetes, and its incidence has more than doubled in the past decade,[3] largely due to the rising prevalence of obesity and type II diabetes.[4] It has been estimated that patients with diabetes have a 12-fold increased risk of end-stage renal disease (ESRD) compared to patients without diabetes.[5] Diabetic kidney disease carries an increased burden in ethnic and racial minorities. Diabetic nephropathy now accounts for about 40% of new cases of ESRD in the United States.[6,7] Between 1992 and 2001, the size of the Medicare CKD population increased by 53%[7] (Figure 3-1), and the adjusted incident rates for diabetes remain high, although the most recent estimates from the United States Renal Data System are stable. Results from the NHANES III study, published in 2002, documented that one-third of patients with diabetes demonstrated either microalbuminuria or macroalbuminuria.[8] Recent data suggest, however, that the rising incidence of diabetic ESRD has not stabilized and may actually be decreasing when compared to growth of the overall diabetic population.[9] The incidence of ESRD due to type I diabetes has been declining for many years,[10] and in certain patients, the early stage of the disease may regress.[11] Kidney involvement and progression, by comparison, vary among ethnic groups in patients with type II diabetes. African Americans with type II diabetes and early nephropathy experience irreversible kidney disease at a higher rate as compared to other groups.[12] In another specific population, the Pima Indians, diabetic ESRD has declined despite a continued rise in the incidence of proteinuria.[13]

Proteinuria and progressive loss of kidney function are the clinical hallmarks of diabetic CKD. The classical view of the natural history of diabetic kidney disease is as follows:[14] proteinuria is preceded by stages of excessive glomerular filtration and of microalbuminuria, which signal an increased risk of progression to overt nephropathy. A progressive increase in proteinuria subsequently leads to a variable decline in renal function. Proteinuria has been thought to signify evidence of glomerular damage and has been viewed as a measure of the severity of diabetic glomerulopathy. Early clinical reports noted nephrotic syndrome in 87% of type I and 70% of patients with type II diabetes, and end-stage renal failure in up to 75% of patients with diabetes within 15 years of developing proteinuria.[6] But recent studies have brought into question both the natural history of diabetic kidney disease and the close link of albuminuria and proteinuria with progression.[15] It has been thought that microalbuminuria is almost always the first sign of diabetic kidney disease, but there are a significant number of biopsy-proven cases of diabetic kidney disease in which albuminuria is absent. Also the exact reasons for proteinuria in diabetes has been brought into question by studies that suggest altered tubular handling of filtered albumin may be playing a significant role in the development of albuminuria.[16]

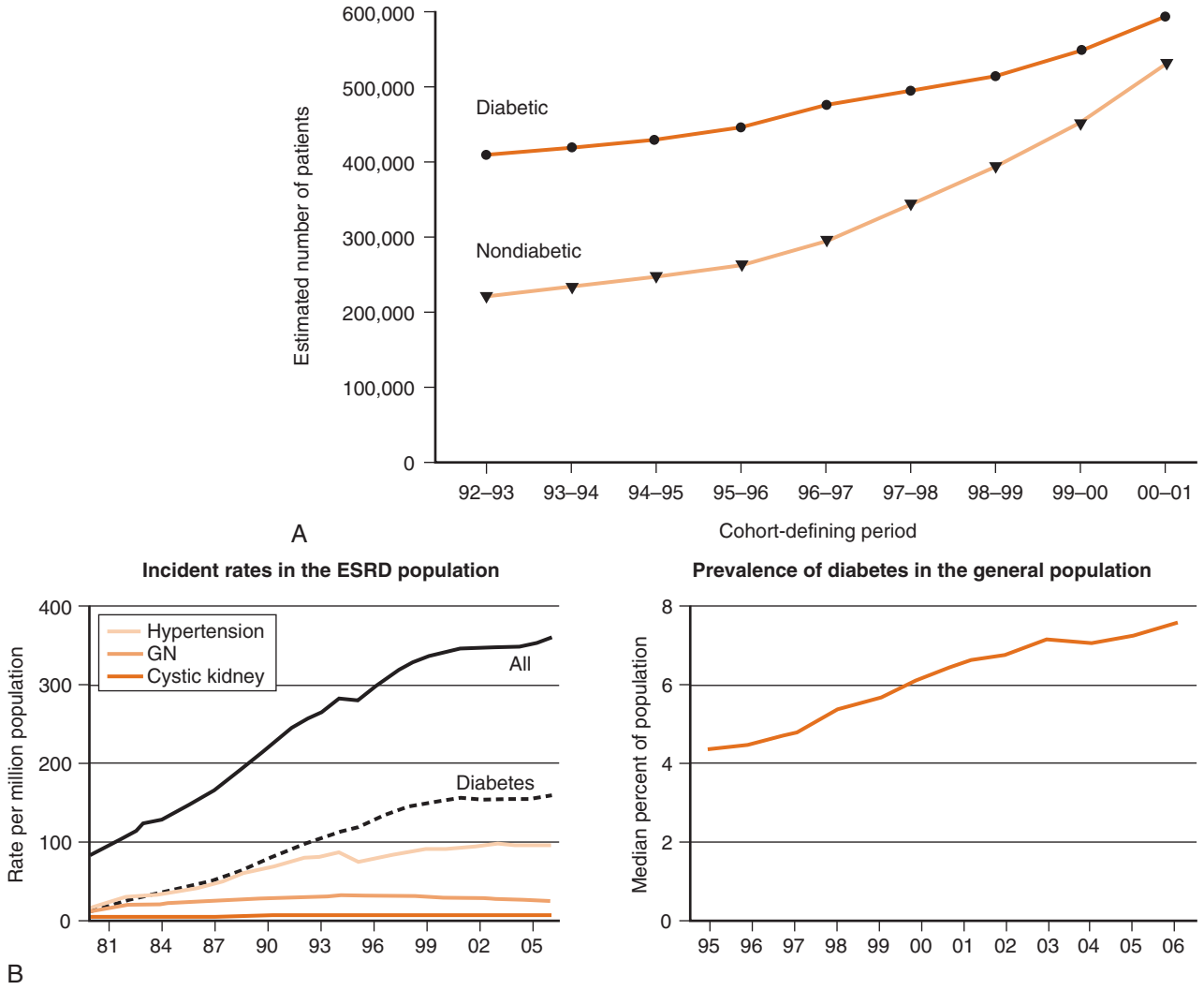


FIGURE 3-1 **A,** Trends in the size of the Medicare CKD population, by diabetic status, from 1992 to 2001. Estimated from patients enrolled in any two consecutive calendar years. **B,** Adjusted incident rates in the ESRD population by primary diagnosis and the prevalence of diabetes in the general population. (**A** from U.S. Renal Data System: USRDS 2003 Annual Data Report, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003. **B** adapted from U.S. Renal Data Systems, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, NIH, NIDDK, Bethesda, MD, 2008).

Factors that cause progression of kidney disease continue to be actively investigated, and they include glomerular hypertension and hypertrophy, local renin-angiotensin activation, activation of coagulation pathways, biochemical damage from hyperglycemia, and lipid deposition. Two decades of progress in retarding the progression of kidney disease have been reviewed by Brenner.[17]

Until the mid-1970s, it was generally accepted that no treatment could slow the progression of diabetic nephropathy.[18] Currently, there is very strong clinical evidence that that the progression of diabetic nephropathy can be slowed dramatically when interventions are implemented at the earliest possible time.[19] Current challenges in the management of the patient with diabetes at risk for developing CKD include nephropathy screening, early interventions to delay progression, and modification of disease comorbidities (Figure 3-2).[20] Later in the course, priorities become prevention of complications of uremia and preparation for renal replacement therapy. Diabetes is a chronic illness, and diabetes care is complex. This chapter reports on the complexity of diabetic nephropathy, on its clinical hallmarks, proteinuria and loss of kidney function, and on its primary therapy, renin-angiotensin system blockade. It details the current approaches to management and describes potential new treatment strategies under current investigation.[21]

EPIDEMIOLOGY AND GENETICS

The realization that 25% to 40% of patients with either type I or type II diabetes will develop diabetic nephropathy[22–25] has led to an ongoing search for risk factors and markers for its development. At this time, the search for biomarkers to identify individuals at higher risk or at preclinical stages of diabetic kidney disease is ongoing.[26] There are at least two goals in these studies: 1) Determine who is at risk for developing diabetic nephropathy, which is defined as the presence of albuminuria or proteinuria or decreasing glomerular filtration rate (GFR); 2) To identify those with diabetic nephropathy who will progress to ESRD. To date

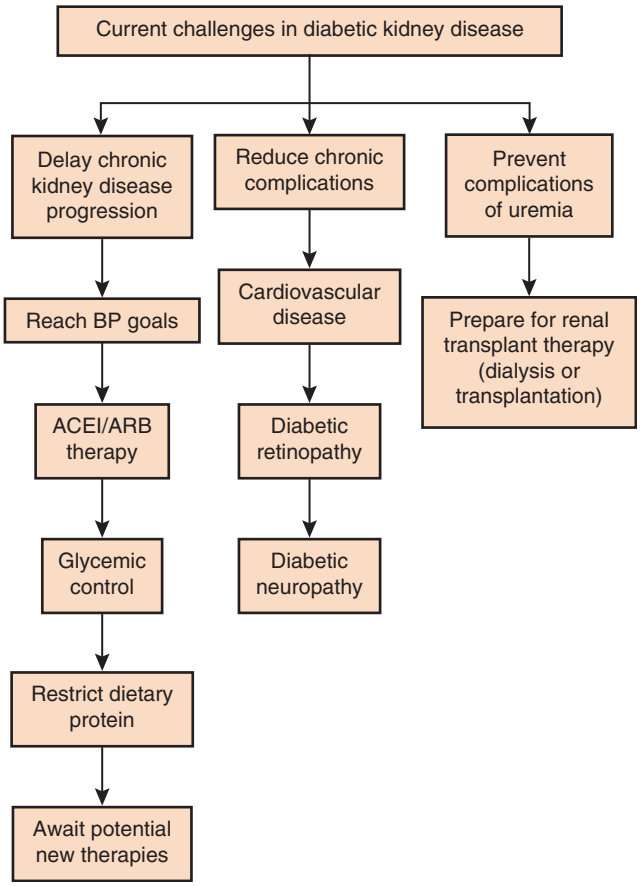


FIGURE 3-2 Current challenges in management of diabetic kidney disease.

no definitive markers have been discovered that are clinically useful to follow either of these very important issues.

There are certain populations who have a higher incidence and prevalence of diabetic nephropathy. Young and colleagues showed that in the United States, African Americans, Hispanics, Asians, and Native Americans all have higher likelihood of having diabetic nephropathy as compared to Caucasians, even when correcting for socioeconomic status, age, and sex.[27] There may even be sex differences within racial groups. Crook and colleagues reported a twofold increase in ESRD in African American women as compared to African American men.[28]

The typical initial manifestation of diabetic nephropathy is detection of urinary albumin above normal levels (microalbuminuria, 30 to 300 mg/24 hours, Table 3-1). It had been thought that microalbuminuria was present in 100% of the cases of diabetic nephropathy. But recent studies show that the initial pattern of expression is changing such that patients will present with increased creatinine and normoalbuminuria.[23] This changing pattern might be due to changes in therapy, as over the past 10 years there has been an increasing recognition of the importance of achieving tight control of blood sugar[29] and maintaining ever lower targets for optimal blood pressure.[30] Importantly, not all patients who develop microalbuminuria will progress. Caramori and colleagues reviewed this, noting that it used to be thought that 80% or more of patients with microalbuminuria will progress to proteinuria and ever worsening renal function. But a number of studies have suggested that closer to 30% to 40% will progress.[23,31,32] In any event, this is still a highly significant number of patients and, as discussed later, they comprise an ever growing number of the population with ESRD.[33] Typically cases of diabetic nephropathy are not seen before 5 years of diabetes in patients with type I diabetes. The incidence then rises over the ensuing 10 years. This observation suggests that a relatively long exposure to the pathophysiological processes associated with diabetic complications is required to cause kidney damage. In contrast, patients with type II diabetes might have diabetic nephropathy at the time of diagnosis. But the duration of diabetes in patients with type II diabetes is unknown in most cases. The incidence and prevalence of diabetic nephropathy may also be changing. Bojestig and colleagues reported that patients who developed diabetes between the years 1961 and 1965 had a cumulative incidence of diabetic nephropathy of 28%, whereas those who developed diabetes between 1971 and 1975 had a cumulative incidence of only 5.8%.[24] Hovind and colleagues recently reported similar findings for diabetic nephropathy and diabetic retinopathy.[34] Although no specific reasons are given for these changes, one might surmise that better blood sugar and blood pressure control might play a significant role. Thus there may be genetic differences that account for why some patients are predisposed to develop diabetic nephropathy whereas others are relatively protected.

Genetic determinants and their impact on the initiation and progression of diabetic nephropathy continue to be actively investigated.[35] The angiotensin converting enzyme (ACE) genotype may influence progression of diabetic nephropathy. Several observational studies have shown that the D allele of the insertion (I)/deletion (D) polymorphism of the ACE gene (ACE/ID) is strongly associated with progressive loss of kidney function.[36] In a recent study of patients with type I diabetic nephropathy, the D allele of the ACE/ID polymorphism was associated with accelerated progression of nephropathy.[37] Analysis of the clinical course of 168 patients who were proteinuric with type II diabetes for 10 years revealed that almost all patients with the DD genotype progressed to ESRD within 10 years.[38] Other studies have indicated that a similar phenomenon occurs in patients with type I diabetes with the D allele. ACE gene

TABLE 3-1 Definitions of Abnormalities in Urinary Albumin and Protein Excretion

	LABORATORY TEST	MICROALBUMINURIA	ALBUMINURIA OR PROTEINURIA
Urine albumin	Spot albumin/creatinine ratio 24-hour collection	17–250 mcg albumin/mg creatinine (males) 25–355 mcg albumin/mg creatinine (females) 30–300 mg/24 hr	>250 mcg albumin/mg creatinine (males) >355 mcg albumin/mg creatinine (females) >300 mg/24 hr
Urine total protein	Spot protein/creatinine ratio 24-hour collection	- -	>0.2 mg protein/mg creatinine >300 mg/24 hr

polymorphism is associated with increased progression even during ACE inhibitor therapy.[39] In contrast, a recent report showed similar beneficial renoprotection from progression of diabetic nephropathy in patients with type I diabetes with ACE II and DD genotypes treated with losartan.[40]

Although there are suggestive studies for a genetic association, no definitive answer is forthcoming. For example, a report from the Pittsburgh epidemiology of diabetes complications study[41] evaluated the relationship for genetic associations with apolipoprotein E, ACE I/D, and lipoprotein lipase *Hind*III polymorphisms with overt diabetic nephropathy (defined as greater than 200μg/min, which is equivalent to greater than 300 mg/24 hours of albumin excretion in the urine). However, associations were only present in certain subgroups. In fact, phenotypic differences in insulin resistance, hypertension, and lipid abnormalities were much stronger predictors.

Considering though the overwhelming likelihood that specific genes are involved in the development and progression of diabetic nephropathy, a national effort has been initiated to address this. The Juvenile Diabetes Research Foundation, the Centers for Disease Control and Prevention, the George Washington University, and the Joslin Diabetes Center made a major commitment to the study of genes and diabetic nephropathy by starting the Genetics of Kidneys in Diabetes (GoKinD) Study to develop a repository of DNA and clinical information on patients with type I diabetes and diabetic nephropathy.[42] Specifically the study was described as follows: "The fundamental aim of GoKinD is to provide a resource to facilitate investigator-initiated research into the genetic basis of diabetic nephropathy. Decisions regarding the genes and chromosomal regions to be studied will be made by individual investigators and subject to a competitive review process." The goal is to recruit 2200 patients with type I diabetes to identify genes that may play a role in the development of diabetic nephropathy. The specific aims of the study are to evaluate genes from: 1) Case trios: 600 patients with type I diabetes with diabetes duration at least 10 years and clinically diagnosed diabetic nephropathy together with their parents; 2) Cases: 500 patients with type I diabetes with diabetes duration at least 10 years and clinically diagnosed diabetic nephropathy for whom parents are not available; 3) Control trios: 500 patients with type I diabetes with normoalbuminuria and diabetes duration at least 15 years together with their parents; 4) Controls: 500 patients with type I diabetes with normoalbuminuria and diabetes duration at least 15 years for whom parents are not available. To date, there have been some possible associations between certain genes and diabetic nephropathy.[43,44] But there are also a series of recent papers showing the lack of association of a number of genes that were thought to be good candidates as markers or predisposing factors for the development or progression of diabetic nephropathy.[45–47]

NATURAL HISTORY

The earliest known manifestation of diabetic nephropathy is the presence of small amounts of albumin in the urine called microalbuminuria. Protein excretion in the urine normally does not exceed 100 to 200 mg/24 hours. Urinary albumin excretion is normally less than 30 mg/24 hours. Although urinary albumin excretion is viewed by some as a continuous variable, the clinical standard remains that excretion of more than 30 mg/24 hours (microalbuminuria) is abnormal. It may be transient due to such circumstances as marked hyperglycemia, hypertension, heart failure, fever, exercise, pregnancy, and medications, or it may reflect the presence of underlying kidney damage. Note that a large intraindividual coefficient of variation may exist.[48] In type I diabetes, and, to a lesser extent, in type II diabetes, the presence of microalbuminuria is a very significant risk factor for progression of kidney disease. For every diabetic individual, microalbuminuria increases risk of the development and progression of hypertension and cardiovascular disease.[49–52] Indeed, the Joint National Committee-VII (JNC-VII) hypertension treatment guidelines list the presence of microalbuminuria (the range is greater than 30 mg/24 hours) as a major risk factor for cardiovascular disease.[53] Glomerular albumin and cardiovascular risk may have in common generalized endothelial dysfunction in diabetes. Persistent microalbuminuria in a patient with diabetes means that the patient has diabetic nephropathy. But not all patients with microalbuminuria progress to higher levels of protein in the urine and a decline in GFR. As discussed earlier, Caramori and colleagues reviewed a number of studies that showed in aggregate that only 30% to 40% of patients with microalbuminuria will progress to overt proteinuria.[23] The principal predictor for progression at this time is the albumin excretion rate, but this is limited as many patients present with increased creatinine and normoalbuminuria. Even in patients with established microalbuminuria, it now appears that a variety of different outcomes are possible: they may progress to overt proteinuria and worse kidney disease, they may stay the same, or they actually may improve. Perkins and colleagues showed that in patients with type I diabetes, there was as much as a 50% chance for regression of microalbuminuria to normal levels.[54] Blood pressure control and lipid control, but not the use of angiotensin-converting enzyme inhibitors, correlated with regression of albuminuria. Thus the approach to microalbuminuria in patients with diabetes is getting more complicated. Because we do not know who will progress, we recommend the following: 1) All diabetic patients should be tested yearly by examining urine for albumin, starting immediately for patients with type II diabetes and after 3 to 5 years for patients with type I diabetes. Although 24-hour urine examinations are certainly ideal, the albumin-to-creatinine ratio (A/C ratio) in a spot urine sample has been shown to be a relatively accurate reflection of the 24-hour urine collection.[55] Thus the A/C ratio may be used both for screening and monitoring; 2) Considering the importance of early, aggressive treatment (tight control of blood sugar, tight control of blood pressure, and use of either ACE inhibitors or angiotensin receptor blockers) should be offered to all patients with persistent microalbuminuria. Moreover, considering the very close association of microalbuminuria with cardiovascular disease, where even people with high levels of urine albumin in the normal range are at increased risk for cardiovascular events as compared to people with lower normal range urine albumin levels,[56] aggressive management of patients with microalbuminuria is indicated for cardiovascular protection and for possible slowing progression of diabetic nephropathy.

Both patients with type I diabetes and patients with type II diabetes with microalbuminuria are at risk for

progression to overt nephropathy. It is now known that patients with type II diabetes who maintain an abnormal albumin excretion rate over 10 years will lose GFR at a rate similar to aging nondiabetics, but with microalbuminuria the GFR decline is faster.[57] Without specific treatment, up to 80% of patients with type I diabetes with sustained microalbuminuria will eventually develop overt nephropathy, as will 25% to 40% of patients with type II diabetes with microalbuminuria.[51] A prospective study in Italy indicated that 4% of patients with type II diabetes with microalbuminuria progressed to overt nephropathy every year.[58] Also of note is a report of decline in kidney function years before the appearance of overt proteinuria, that is, during the microalbuminuric stage, in one third of a cohort of type I diabetic patients.[59]

Proteinuria is now understood to be not only a marker of renal pathophysiology, but is also linked to declining kidney function, systemic endothelial dysfunction, and cardiovascular mortality. First observed in diabetic patients over a century ago, clinical proteinuria was described in a pathological report of diabetic glomerulosclerosis by Kimmelstiel and Wilson in 1936.[60] The natural sequence of proteinuria followed by loss of kidney function was not described until decades later. Diabetic proteinuria results from complex derangement in the glomerular filtration barrier, including endothelial cells, the basement membrane, and the podocyte.[61] The natural history of diabetic nephropathy, including changes in glomerular filtration and proteinuria and stages of preventative treatment, is shown in Figure 3-3. Of note, kidney disease in type II diabetic patients is heterogenous and may not be associated with albuminuria. According to an analysis of the 1988-1994 NHANES data, up to 36% of diabetic patients with impaired GFR had neither micro- nor overt albuminuria, presumably related to either nondiabetic kidney disease or diabetes-related disease apart from glomerulosclerosis.[62] The average time to onset of proteinuria from the diagnosis of diabetes in type I patients is 19 years; the interval is shorter but variable in type II patients. Several definitions of persistent proteinuria in diabetes are now in use (see Table 3-1). Diabetic proteinuria refers to albuminuria and to increased total urinary protein excretion.[63] Yearly increases in protein excretion average about 20%, but wide standard deviations exist. Untreated, up to three fourths of patients who are proteinuric with type I or type II diabetes may become nephrotic.[64] Progressive loss of kidney function occurs over several years without intervention in patients with type I diabetes. The overall sequence is similar in patients with type II diabetes (Figure 3-4),[65] but the exact onset of diabetes may be uncertain, pathology not related to or atypical for diabetic nephropathy may exist, and the decline in function may be more variable. In its most advanced stages, diabetic glomerular proteinuria becomes less selective, with a significant contribution from large proteins such as albumin and immunoglobulin G (IgG), and with tubular proteinuria.

Much progress has been made in the past 20 years in slowing progression of diabetic kidney disease to ESRD. But in spite of this progress, an ever increasing number of patients progress to renal failure. Diabetes has become the major cause of ESRD, accounting for 45% of the new cases (about 42,000 cases) in 2001 (hypertension and glomerulonephritis are second and third, respectively). The percentage of new cases of ESRD due to diabetes has been rising steadily over the last 25 years. At least in the last 20 years, this continual increase in the numbers of patients with ESRD due to diabetes is largely due to the epidemic of type II diabetes that is occurring in the United States and throughout the world (see Figure 3-1, B). The numbers of patients with ESRD is expected to double over the next 7 to 10 years, mostly due to diabetic nephropathy. Although all patients with ESRD have significantly greater rates of morbidity and mortality, the patients with diabetes and

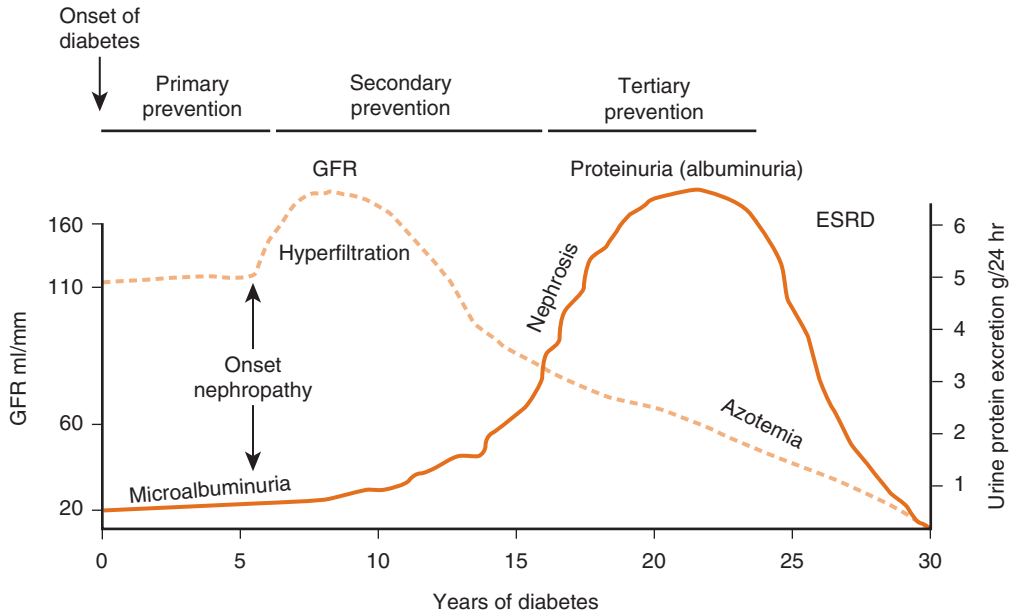


FIGURE 3-3 The natural history of diabetic kidney disease. Changes in glomerular filtration rate (GFR) and microalbuminuria/proteinuria are shown. Progressive loss of kidney function occurs over years, without successful intervention. Following the onset of diabetes in susceptible individuals, treatment of diabetic nephropathy may be primary (reduce the development of microalbuminuria), secondary (prevent the transition to overt nephropathy), or tertiary (slow the progression of established nephropathy to ESRD).

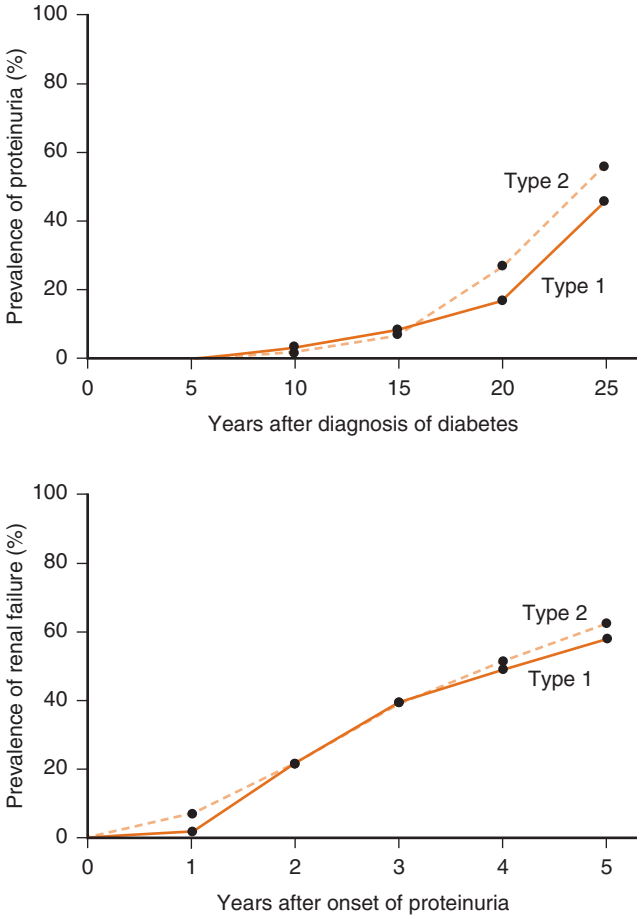


FIGURE 3-4 Proteinuria and progression to ESRD in diabetic nephropathy in type 1 and type 2 diabetic patients. Similar rates of proteinuria and time of progression from onset of proteinuria to kidney failure may occur in both types of diabetes. (Adapted from E. Ritz, S.O. Orth, Nephropathy in patients with type 2 diabetes mellitus, N. Engl. J. Med. 341 [1999] 1127-1133.)

ESRD provide an even greater challenge as the often concurrent conditions of peripheral vascular disease, neuropathy, and progressive cardiovascular disease greatly affect lifestyle and often shorten life expectancy significantly.

Cardiovascular disease frequently complicates the natural history of diabetic kidney disease. The pivotal involvement of the renin-angiotensin system (RAS) in the pathophysiology of both diabetic renal and cardiovascular disease has been extensively reviewed.[66] Biological functions of angiotensin are important for the homeostasis of the cardiovascular system. With similar features of the kidney and systemic vasculature, elevated urinary albumin excretion is felt to reflect damage to both the glomerulus and blood vessels. As with the underlying diabetes, diabetic vasculopathy is multifactorial.

Kidney disease is an independent risk factor for cardiovascular disease,[67] placing an individual with CKD in the same category of cardiovascular risk as diabetes itself. Microalbuminuria has been shown to increase the risk for cardiovascular events including stroke, myocardial infarction, and mortality.[68,69] Long-term studies indicate that microalbuminuria in patients with diabetes predicts not only subsequent clinical proteinuria, but also increased mortality that is primarily cardiovascular.[69] Clinically, microalbuminuria is associated with a variety of cardiovascular risk factors, including hypertension, insulin resistance, atherogenic dyslipidemia, and obesity. The Framingham Heart Study first demonstrated that relevance of proteinuria to cardiovascular prognosis.[70] A study of type II diabetes confirmed higher mortality associated with proteinuria.[71] Over a 5-year period, 37% of diabetics with proteinuria died, compared to 8% without nephropathy. Mortality was directly related to proteinuria, with a 36% increase in risk for each log unit increase in proteinuria. The fivefold excess risk for cardiovascular mortality in this group was independent of other risk factors including creatinine, age, and glycemic control. The risk of cardiovascular disease associated with diabetic kidney disease was also demonstrated in an observational study of 3608 patients enrolled in a multivessel coronary artery disease registry.[72] Among patients without diabetes, mortality at 7 years was 12% among patients without CKD and 39% among patients with CKD (serum creatinine > 1.5 mg/dl) (Figure 3-5). Among diabetic patients without CKD, mortality was only slightly higher than for nondiabetic patients with kidney disease. However, when both diabetes and CKD were present, the mortality risk was additive at 70% during the 7-year observation period.[72]

As indicated in Figure 3-3, treatment of diabetic nephropathy may be primary (reduce the development of Microalbuminuria),

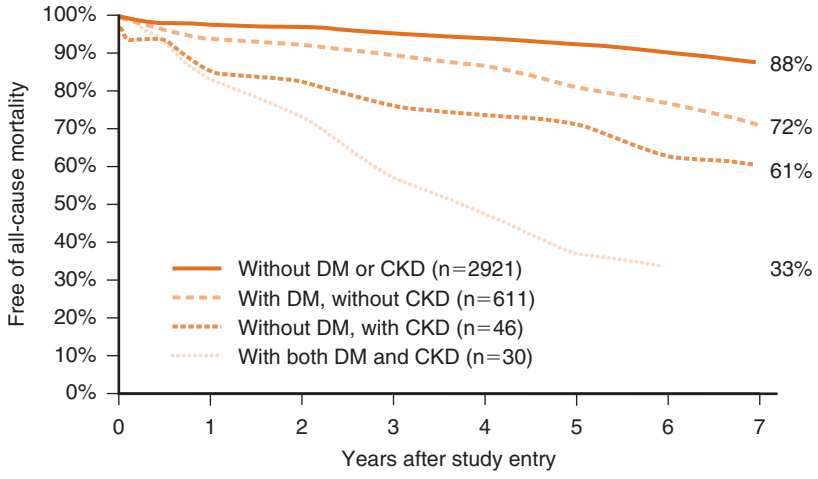


FIGURE 3-5 Survival curves (all-cause mortality) for cohorts of patients defined by CKD and diabetes mellitus (DM). (Adapted from L.A. Szczech, P.J. Best, E. Crowley, et al., for the Bypass Angioplasty Revascularization Investigation [BARI] Investigators: Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation, Circulation 105 [2002] 2253-2258.)

secondary (prevent the transition to overt nephropathy), or tertiary (slow the progression of established nephropathy to ESRD).[73]

MECHANISMS

Diabetic proteinuria reflects glomerular damage and increased glomerular permeability to macromolecules, although the exact molecular mechanisms are still being defined. In general, protein permeability across the filtration barrier is known to be affected by the hemodynamic pressure gradient across the glomerular basement membrane and separate factors involving the filtration barrier itself, including the glomerular filter surface area and its size- and charge-selectivity. In diabetic nephropathy, both hemodynamic and intrinsic basement membrane factors contribute to proteinuria.[3] For example, angiotensin II combines hemodynamic actions such as induction of systemic vasoconstriction, increased glomerular arteriolar resistance, and increase in glomerular capillary pressure, with nonhemodynamic actions such as increased glomerular capillary permeability, reduction in filtration surface area, enhancement of extracellular matrix proteins, and stimulation of renal proliferation and fibrogenic chemokines, including monocyte chemoattractant protein-1 and transforming growth factor-B (TGF-B). The role of these factors in CKD progression was recently reviewed.[74]

Although some pathological changes characteristic of diabetic glomerulosclerosis (Figure 3-6), such as increased basement membrane width and mesangial expansion, are known to precede the development of diabetic proteinuria, other changes, including mesangial and interstitial expansion, correlate with the degree of albuminuria. The structural basis for the protein passage resides either in the glomerular basement membrane or the nearby epithelial cell layer. Two adjacent molecular filters are felt to control glomerular permeability: the basement membrane itself, and the slit diaphragm (Figure 3-7). The glomerular basement membrane in humans is a complex tripartite structure of endothelial cells with fenestrations, dense basement membrane fibrils, and the outer visceral podocyte cells. The slit diaphragm arises between the interdigitating foot processes of the podocytes.

Hyperglycemia may cause kidney damage through factors such as advanced glycation product accumulation, increased expression of growth factors, and activation of inflammatory factors. Glomerular hypertension, favorable in the short-term, creates detrimental long-term nonhemodynamic consequences. According to a dominant theory of diabetic nephropathy based on animal models, glomerular hemodynamic forces lead to upregulation of fibrotic and inflammatory processes, resulting in structural damage.[75] The progression from normoalbuminuria to overt proteinuria in diabetes correlated in one study with a reduction in size and charge selectivity of the filtration barrier,[76] and in other studies with a reduction in slit-pore density. More recent investigation has emphasized the role of extracellular matrix proteins[77] and podocyte injury and loss, which are prominent ultrastructural abnormalities and hallmarks of proteinuric conditions such as diabetic nephropathy.[78] Glomerular podocyte numbers are decreased in diabetics.[79] One analysis revealed decreased podocyte density and increased foot process width in glomeruli of patients with type II diabetes with proteinuria.[80] Several mechanisms of podocyte loss have been speculated, including modulation of nephrin expression.[81] This transmembrane protein gene product is localized to the filtration slit area between podocyte foot processes and is integral to the formation of the zipper like slit diaphragm structure. A recent study reported decreased protein levels of nephrin and podocin, despite an increase in their glomerular mRNA levels, for several acquired human diseases including diabetic nephropathy.[82] Some human data suggest a down-regulation of nephrin expression in both type I and type II diabetic nephropathy.[83,84] Nephrin gene expression may be inversely related to the amount of proteinuria.[85] Podocin mutations have also been described in a variety of proteinuric conditions.[86] Growing evidence indicates that endothelin contributes to podocyte injury in diabetic nephropathy. Both hyperglycemia and angiotensin II are inducers of endothelin production.[87] The participation of inflammatory mediators in the pathogenesis of diabetic nephropathy has been proposed.[88] In addition to the concept that increased protein permeability accounts for diabetic proteinuria, a defect in tubular albumin retrieval has been recently been postulated.[89] The hypothesis in this model is that as much as 2 grams of albumin are routinely filtered by the glomeruli and that proximal tubular cells absorb the albumin, and albumin fragments are secreted into the tubular fluid. From studies in animals and humans, the researchers postulate that diabetes leads to a defect in the normal processing of

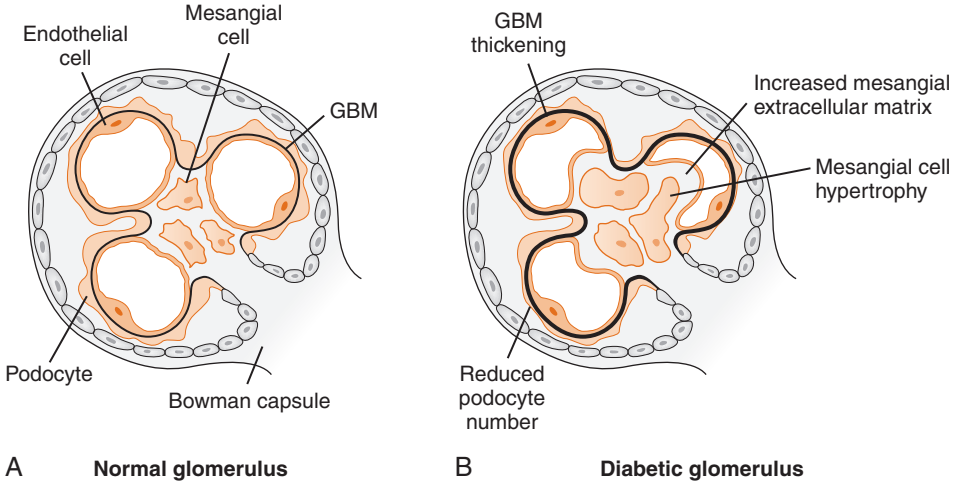


FIGURE 3-6 Pathological changes characteristic of diabetic glomerulosclerosis. (Reprinted with permission from J.A. Jefferson, S.J. Shankland, R.H. Pichler, Proteinuria in diabetic kidney disease: a mechanistic viewpoint, Kidney Int. 74 [2008] 22-36.)

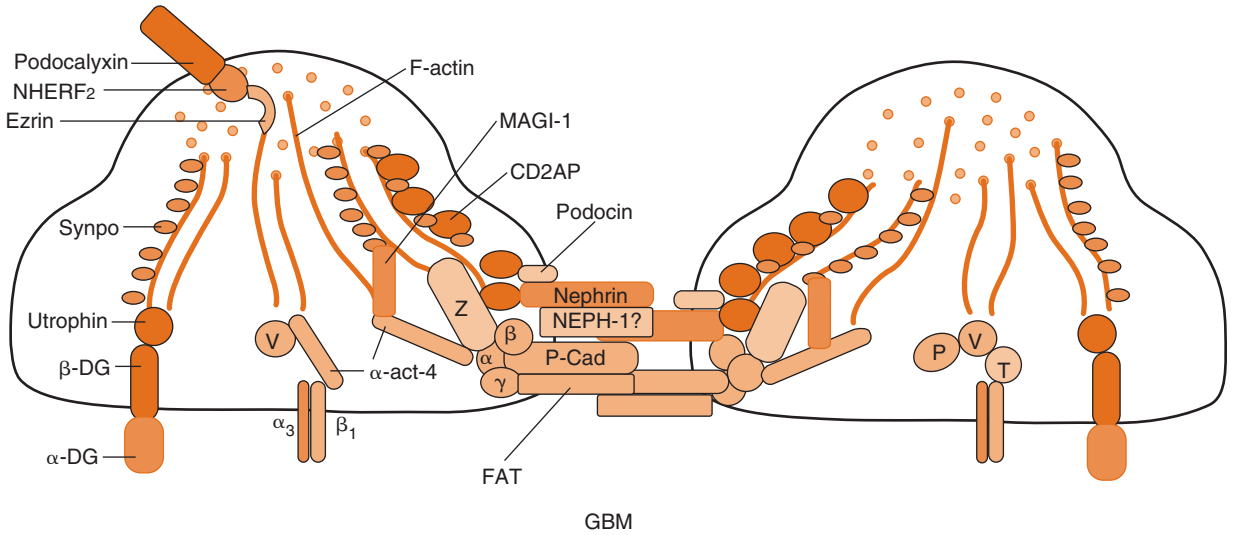


FIGURE 3-7 The barrier to proteinuria. Schematic drawing of the visceral glomerular epithelial cells (podocytes) lining the outer aspect of the glomerular basement membrane. Foot processes are connected by the slit diaphragm with nephrin, podocin, and other proteins. Proposed mechanisms of diabetic proteinuria include structural changes to the basement membrane, hemodynamic injury to podocytes, decreased number of podocytes, damaged slit diaphragm components, and reduced expression of nephrin. (Adapted from P. Mundel, S. Shankland, Podocyte biology and response to injury. J. Am. Soc. Nephrol. 13 [2002] 3005-3015).

filtered albumin that leads to an increase in intact urinary albumin.[89] Tubulointerstitial fibrosis is also increasingly recognized as a uniform feature of diabetic nephropathy and predictor of renal failure. Indeed, there is a growing literature focusing on the tubular cell damage and interstitial fibrosis for being of primary importance in the pathogenesis of diabetic nephropathy.[90,91]

A variety of experimental models and human kidney diseases have now indicated that proteinuria should be accepted as an independent and modifiable risk factor for renal disease,[92] and other studies have linked proteinuria to risk of ESRD and renal death.[93] Evidence suggests that proteinuria may be a reversible process. Proteinuria as a predictor of renal progression in human diabetic nephropathy has become a key clinical issue. One limitation is the inherent intraindividual variability in urinary excretion of total protein or albumin,[94] up to a standard deviation of up to 50%. Nonetheless, heavy proteinuria doubled the risk of progression in the Collaborative Study Group trial of Captopril in patients with type I diabetes[95] and may contribute to morality risk.[96] Of two more recent well-known studies in patients with type II diabetes, the Irbesartan Diabetic Nephropathy Trial (IDNT)[97] and Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL),[98] proteinuria was a prospective outcome measure only in the latter. Although no relationship of baseline proteinuria to renal outcomes was included in the original report, subsequent analyses reported proteinuria to be the most important predictor of ESRD.[99,100] For the IDNT, unpublished data revealed an increased risk of progression when baseline proteinuria was 3 grams or more per 24 hours.[101]

Although there is no proof of concept from clinical interventional trials that specific titration against the level of proteinuria improves the efficacy of renoprotective therapy, many consider remission (<1 g/day) of proteinuria to be a valid intermediate goal.[17] Targeting proteinuria reduction in patients with established diabetic nephropathy to slow progression is generally accomplished with agents that reduce both blood pressure and proteinuria. Data are very limited on therapies that might reduce proteinuria through other primary mechanisms, without correcting hypertension.

Diabetic nephropathy is a disease model for the potential use of proteinuria as a surrogate end point.[102] Because early intervention is critical in diabetic nephropathy, a surrogate marker would be valuable.[103] However, disadvantages include intraindividual variability in proteinuria, uncertainty regarding meaningful reduction in proteinuria, and the lack of drugs with specific antiproteinuric effects to be tested. The relationship of proteinuria to the course of diabetic nephropathy is complex, and strict interpretation of available data does not readily lead to a specific goal for proteinuria reduction. Finally, evidence is emerging that diabetic CKD often develops in the absence of proteinuria. For example, more than half of adults with type II diabetes and decreased estimated GFR do not have albuminuria.[62] In the Atherosclerosis Risk in Communities (ARIC) study, one third of incident CKD occurred in individuals without albuminuria.[104] The observed positive association between glycemic control and incident CKD was present even in those without proteinuria.

TREATMENT

Blood Sugar Control

Many studies have demonstrated the critical importance of tight control of blood sugar in preventing the development or slowing the progression of diabetic nephropathy.[105–108] The importance of tight control was definitively shown for patients with type I diabetes in the Diabetes Complications and Control Trial (DCCT) study.[105] In the initial study,

1441 patients with type I diabetes mellitus were evaluated for a mean of 6.5 years. The patients received either conventional therapy, which at that time meant an average hemoglobin A1c (Hgb A1c) of 9.1, or intensive therapy, with a median Hgb A1c of 7.2. Intensive therapy led to a decrease in the development of microalbuminuria by 39% and led to a decrease in progression from microalbuminuria to overt proteinuria (defined as greater than 300 mg/24 hours) by 54%. Critical follow-up studies have continued to show the benefit of tight control of blood glucose in patients with type I diabetes. At the end of the DCCT, the patients in the conventional-therapy group were offered intensive therapy, and the care of all patients was transferred to their own physicians. Nephropathy was evaluated based on urine specimens obtained from 1302 patients during the 3rd or 4th year after the end of the original DCCT study, approximately half of whom were from each treatment group. The median glycosylated hemoglobin values were 8.2% in the former conventional therapy arm and 7.9% in the former intensive therapy arm. Nevertheless, new cases of microalbuminuria were detected in 11% of 573 patients in the former conventional-therapy group, compared to 5% of 601 patients in the former intensive-therapy group, representing a 53% odds reduction. The risk of new albuminuria was reduced by 86% in the intensive-therapy group. Thus the importance of early aggressive management of blood sugar is clearly demonstrated in this study. It is quite common for blood glucose control to worsen over years of diabetes mellitus therapy. This worsening blood glucose control likely reflects a combination of decreasing effectiveness of insulin due to multiple factors (e.g., changing metabolic requirements, resistance to effects of injected insulin, difficulty in maintaining the strict intensive regimen, age of the patient, genetic factors, and other as yet unanticipated factors). But even with worsening in the Hgb A1c, there were still benefits from keeping the blood sugar as tightly controlled as possible. The DCCT study group recently reported on a 8-year follow-up study[109] (EDIC). As with the 4-year follow-up study, there was a narrowing of the Hgb A1c values comparing the original intensive therapy group (Hgb A1c of 8.0%) to the conventional therapy group (Hgb A1c of 8.2%). Yet there was still a 57% risk reduction for the development of microalbuminuria in the original intensive therapy group compared to the conventional group. The risk reduction for progression to overt proteinuria from microalbuminuria was 84% in the intensive therapy group. According to follow-up analysis of DCCT data, Hgb A1c variability was greater in the conventional glucose control group and independently added to the average level of glycemia in predicting risk of progression to nephropathy.[110] These results strongly support the recommendation of early and aggressive management of blood sugar as a highly effective approach in slowing the development and progression of diabetic kidney disease.

Patients with type II diabetes also greatly benefit from tight control of blood sugar. The United Kingdom Prospective Diabetes Study (UKPDS) trial was designed to explore the importance of control of blood sugar in type II diabetic patients.[108] In this very large study, the conventional therapy group averaged a Hgb A1c of 7.9%, whereas the intensively treated group had a Hgb A1c of 7.0%. The risk reduction in developing microalbuminuria over 15 years was 33% for the intensive treatment group. The risk reduction for progression of microalbuminuria to proteinuria was 42%. Indeed the risk reduction for doubling of creatinine was 67%. The ARIC study prospectively followed 1871 adults with diabetes for 11 years and confirmed that high Hgb A1c was associated with higher risk of CKD.[104] Considering the impressive results from both the DCCT and the UKPDS, the American Diabetes Association's official position is that all patients with diabetes should aim for a Hgb A1c of less than 7% to reduce the risk of diabetic nephropathy.[109]

Hypertension

Both hypertension and diabetes mellitus are risk factors for CKD.[111] In the United States alone, at least 11 million patients with diabetes, and 60% of all those with diabetes have hypertension. It has been emphasized that the risks of elevated blood pressure are greater for the diabetic than for the nondiabetic population.[112] Sixty percent of hypertensive patients with type II diabetes develop diabetic kidney disease; however, hypertension for the majority of patients is inadequately controlled.[113] Both systolic and diastolic hypertension accelerate the progression of microvascular complications such as nephropathy[114] and cardiovascular complications of diabetes, including early-carotid atherosclerosis as determined by intimamedia thickening.[115] Even high-normal blood pressure levels place patients in a high risk category.[116] Hypertension induces renal oxidative stress in animal models of early diabetes.[117] Overall, the prevalence of hypertension in the diabetic population is at least double that in the nondiabetic population (Table 3-2). The causes are complex and likely multifactorial (Figure 3-8).

Although hypertension is a typical manifestation of kidney disease, for 2 decades it has also been recognized as an early abnormality of nephropathy.[118] Blood pressure elevations commonly precede or occur concurrent with microalbuminuria in patients with type I and type II diabetes.[119] Increased blood pressure has a major role in the development of proteinuria in diabetes.[120] Hypertension may also be associated with the insulin resistance syndrome. In addition to genetics, several other factors contribute to hypertension in diabetic patients.[121] Intensive insulin treatment with near normal glycemia reduces the incidence of hypertension, an effect shown by the DCCT to be sustained for years after intensive treatment has stopped.[109] In general, hypertension in both type I and type II diabetes is characterized by expanded plasma volume, increased peripheral vascular resistance, and suppressed plasma renin activity. Systolic hypertension has

TABLE 3-2 Prevalence of Hypertension in Diabetes Mellitus

DIABETES TYPE	STAGE	PREVALENCE
1	No proteinuria	44%
	Proteinuria	67%
	Elevated serum creatinine	92%
2	No proteinuria	70%
	Proteinuria	83%
	Elevated serum creatinine	100%

(From E. Ritz, et al: Hypertension and vascular disease as complications of diabetes, in: Laragh JH, Brenner BM [Eds]: Hypertension: Pathophysiology, Diagnosis, and Management, Raven Press, New York, 1990.)

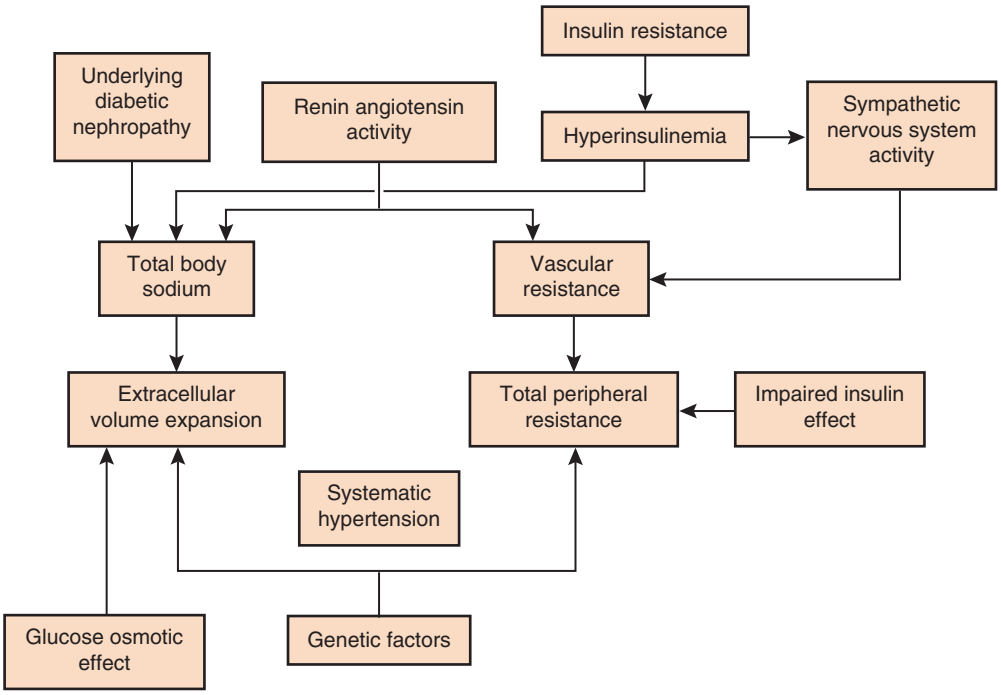


FIGURE 3-8 Mechanism of hypertension in diabetic kidney disease.

been attributed to loss of elastic compliance in atherosclerotic large vessels.[19] In patients with type I diabetes, a rise in systemic pressure may precede the presence of kidney impairment, becoming manifest about the time the patient develops microalbuminuria or even prior to a rise in urinary albumin excretion.[122] Microalbuminuria and its progression to overt nephropathy are associated with further increases in blood pressure.[123] In type II diabetes, overt hypertension or more subtle circadian blood pressure abnormalities are frequently present prior to the development of proteinuria, so that many patients with microalbuminuria have hypertension.[124] In fact, hypertension is present at the time of diagnosis of type II diabetes in about one third of patients.[19]

Diabetic kidney disease may lead to hypertension through direct actions on renal sodium handling and alterations in vascular compliance.[125] An association between the level of blood pressure and the clinical hallmarks of diabetic nephropathy, both the degree of albuminuria[126] and CKD progression, has been recognized for many years. In the last two decades, both observational and interventional studies have revealed that inadequately treated hypertension is a key contributor to loss of renal function, in both patients with type I and patients with type II diabetes.[127] In a recent study, each 10 mmHg increase in blood pressure was associated with a loss of about 1 cc/minute in GFR per year.[128] Both systolic and diastolic blood pressure are associated with albuminuria in diabetes.[129] Baseline systolic blood pressure was recently shown to be a stronger predictor of nephropathy than diastolic pressure in the RENAAL study of patients with type II diabetes.[130]

Reports initially establishing the benefit of aggressive blood pressure control on slowing the decline in GFR did not emphasize that rising proteinuria was reversed and then reduced to less than 50% of the pretreatment value (Figure 3-9).[131] This and similarly important early studies showing that effective blood pressure control reduces proteinuria and slows renal progression have been corroborated.[75,132] In a model of genetic hypertension and diabetes, prevention of hypertension restores nephrin and prevents albuminuria.[133] For both primary and secondary prevention of CKD progression in diabetic patients, clinical trials and metaanalyses have now demonstrated the beneficial effects of normalizing blood pressure.[134] A recent posthoc analysis of the BENEDICT trial demonstrated that blood pressure control in patients with type II diabetes who were nonalbuminuric was able to prevent progression to microalbuminuria.[135] More recently, the effect of intensive blood pressure control on the course of type I diabetic nephropathy was evaluated in patients who had participated in the Collaborative Study Group Captopril Study.[136] With an average 6 mmHg difference in mean arterial pressure (MAP) over 24 months using ramipril in combination with other agents, proteinuria decreased by half in the intensive blood pressure group (MAP $\leq$92 mmHg) and increased by about 50% in the less intensive group (MAP 100 to 197 mmHg). Rates of decline in renal function during the intervention did not differ. Aggressive blood pressure treatment also induced remission of proteinuria and slowed decline of renal function in a prospective trial of 300 patients with type I diabetes, with a MAP of 100 mm Hg achieved predominantly with ACEI.[137] The relevance of intensive blood pressure control (mean blood pressure 128/75 mmHg) versus conventional control (mean blood pressure 137/81 mmHg) to nephropathy progression in patients with type II diabetes was evaluated by Schrier and colleagues.[138] Fewer intensively treated patients developed microalbuminuria or progressed to overt albuminuria. Intense blood pressure lowering (<125/75 mmHg) in normotensive patients with type II diabetes also prevented progression of microalbuminia.[139] Growing evidence suggests that significant proteinuria is associated with cardiovascular disease in patients with diabetes, so

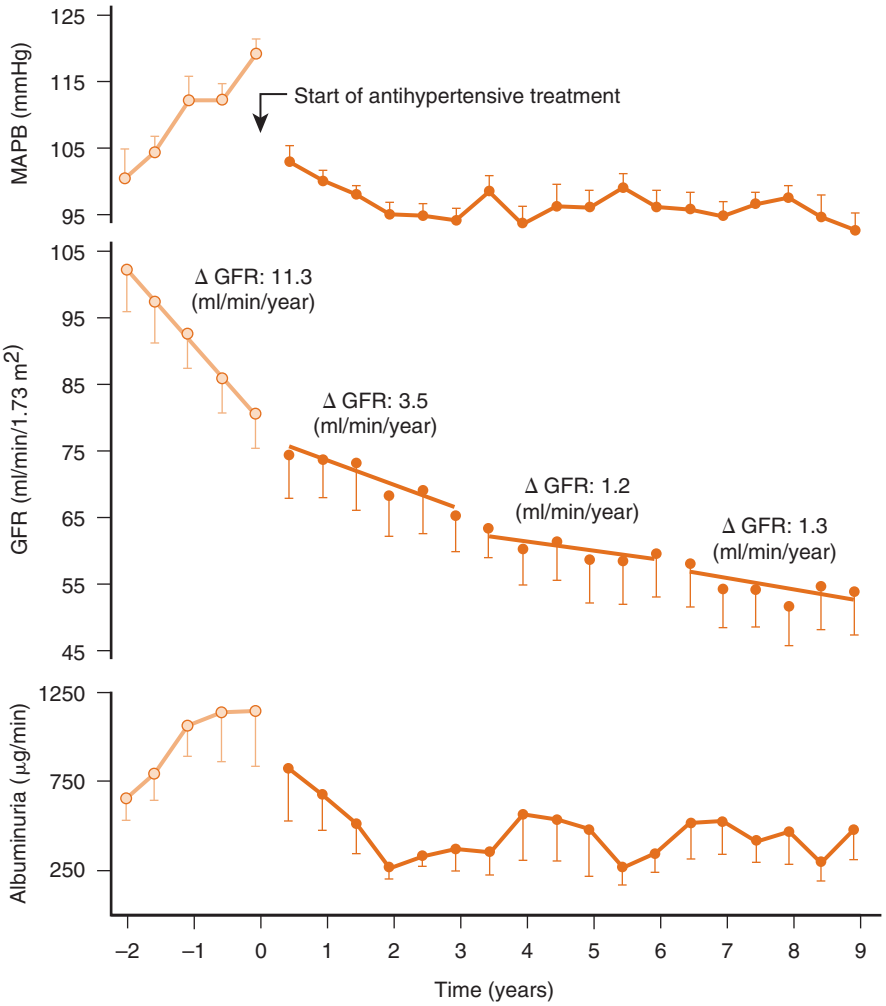


FIGURE 3-9 Early report by Parving and others on the benefit of antihypertensive treatment on kidney function in diabetic nephropathy. With a fall in average blood pressures in nine patients from 143/96 mm Hg to 129/84 mm Hg, albuminuria was reduced by 50%. (Adapted from H.H. Parving, A.R. Andersen, U.M. Smidt, et al., Effect of antihypertensive treatment on kidney function in diabetic nephropathy, BMJ 294 [1987] 1443-1447.)

that proteinuria reduction may add to cardiovascular risk reduction associated with hypertension control. Effective antihypertensive management is generally regarded as the best inhibitor of diabetic nephropathy progression, almost regardless of the class of agent used. When antihypertensive therapy is initiated, an initial drop in kidney function may typically occur.[140] Reductions in pressure are associated with lowering of glomerular capillary pressure and diminished proteinuria.[141]

The appropriate blood pressure at which to initiate therapy and the target blood pressure goal are widely debated topics. Current recommendations based largely on type II diabetes studies suggest targets for diabetic patients that are lower than for the general population.[142] Based on available evidence that blood pressure readings above 125/75 mmHg increased the risk of ESRD in diabetic patients, a consensus statement from the National Kidney Foundation published in 2000 advised treatment goals of less than 125/75 mmHg.[143] Since then, several expert panels including the National Kidney Foundation and the American Diabetes Association have adopted blood pressure targets of less than 130/80 mmHg as optimal for renal and cardiovascular protection in the diabetic patient with nephropathy (Table 3-3).[116,144–146] A combination regimen of three or more drugs may be required. Clinical trial data suggest that MAPs of 92 mmHg or lower (corresponding to a blood pressure of about 130/70 mmHg) achieve greater preservation of renal function. It should be noted that these revised blood pressure targets were not consistently achieved in the earlier landmark studies of ACEI and angiotensin receptor blockers (ARBs) in diabetic nephropathy patients.[147] It is generally accepted by hypertension specialists that systolic pressure, and even perhaps pulse pressure, are better goals for treatment than diastolic pressure. Targets for high levels of isolated systolic hypertension (<180 mmHg) are less certain; systolic pressure should be lowered gradually, as tolerated.[148] Blood pressure evaluation should also take into account 24-hour pressures and the nocturnal dipping status (nondipping or reverse dipping), as determined by ambulatory monitoring.[149] One study reported that normotensive patients with type II diabetes and normo- or microalbuminuria had less progression of albuminuria if blood pressure was lowered further to less than 120/80 mmHg (using an ARB).[139] In patients with type II diabetes with normoalbuminuria and hypertension, effective blood pressure reduction protects against the development of microalbuminuria.[139] Unlike glucose control, tight blood pressure control does not appear to have a "legacy" effect in diabetic patients, with optimal outcomes requiring sustained maintenance of blood pressure control.[150] In summary, blood pressure goals will need to be tailored to the

TABLE 3-3 Recent Blood Pressure Management Guideline Targets issued by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), the World Health Organization-International Society of Hypertension (WHO-ISH), the National Kidney Foundation (NKF), and the American Diabetes Association (ADA)

YEAR	SOURCE	PATIENT POPULATION	TARGET BP	NOTES
1997	Sixth report of the Joint National Committee for prevention; Detection evaluation and treatment of high blood pressure (JNC-VI)	Chronic kidney disease or diabetes mellitus	<130/<85	If diabetes or kidney disease
1999	World Health Organization/International Society for Hypertension (WHO/ISH)		<130/<85	
2000	National Kidney Foundation Special Report	Chronic kidney disease	<130/<80	<125/<75 for proteinuria >1 gm/day and renal insufficiency
2000	American Diabetes Association	Chronic kidney disease, diabetes mellitus	<130/<85	For isolated systolic hypertension and systolic blood pressure >180 mm Hg, lower BP in stages
2003	Seventh report of the Joint National Committee for prevention, detection, evaluation and treatment of high blood pressure (JNC-VII)	Chronic kidney disease or diabetes mellitus	<130/<80	For diabetes or chronic kidney disease (GFR <60 ml/min/1.73 m^2 or albuminuria)
2003	American Diabetes Association	Chronic kidney disease or diabetes mellitus	<130/<80	
2004	National Kidney Foundation K/DOQI Clinical Practice Guidelines on hypertension and antihypertensive agents in CKD	Diabetic kidney disease	<130/<80	

(Modified with permission from G.L. Bakris, The evolution of treatment guidelines for diabetic nephropathy, Postgrad. Med. 113 [2003] 35-50.)

individual patient, based on tolerability and the likelihood that risk of renal progression involves a continuous, and not dichotomous, relation to blood pressure levels.[147]

The optimal level of blood pressure decrease to achieve cardiovascular risk reduction is unclear,[151] but it may be answered by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial on cardiovascular risk reduction in high risk patients with type II diabetes. Although the intensive blood glucose reduction arm has been stopped due to safety concerns, the study of the effects of aggressively lowering blood pressure are ongoing through 2009.[152] Though data to evaluate the risks associated with low ranges of systolic blood pressure in diabetic kidney disease are not sufficient, pressures less than 100 to 110 mmHg should be avoided. Paradoxically, the fear of reducing systemic pressures too far may have contributed to failure to achieve lower blood pressure goals. Nonetheless, three large studies, the Systolic Hypertension in the Elderly Program (SHEP),[153] the Hypertension Optimal Treatment (HOT) trial,[154] and the United Kingdom Prospective Diabetes Study (UKPDS)[155] have supported the notion that aggressive blood pressure lowering may not be harmful. Data suggest that reduced arterial stiffness may be associated with use of ACEI, ARBs, and calcium channel blockers.[156]

Several studies have underlined the challenge of achieving blood targets even in the clinical trial setting.[157] In the RENAAL study, for example, although systolic blood pressure was a stronger predictor of renal outcomes than diastolic pressure, less than half of patients achieved blood pressure goals during the treatment phase.[130] Hypertension may require selections from several different classes of drugs, and there are special considerations in the choice of antihypertensive treatment for the hypertension diabetic (Table 3-4). Recent clinical trials have confirmed the poor response of diabetic nephropathy to treatment. An analysis of the NHANES III data base indicated that only 11% of diabetic nephropathy patients being treated for hypertension achieved blood pressure goals of <130/85 mm Hg.[158] Furthermore, over a third of patients in ARB clinical trials with type II diabetic nephropathy progressed to primary renal endpoints.[97,98] In a recent trial implementing a stepped-care approach treatment algorithm, centered on maximal doses of ACEI or ARBs, only one-third of patients reached target blood pressures of less than 130/80 mm Hg.[121] Target systolic blood pressure levels were even more difficult to control. A recent report of hypertensive military veterans indicated that, for patients with diabetes and renal disease, blood pressure

TABLE 3-4 Special Considerations in the Selection of Antihypertensive Medications for the Diabetic Patient

DRUG CLASS	SPECIAL CONSIDERATIONS
Diuretic	Edema common in diabetic nephropathy; thiazides not effective in renal insufficiency
Angiotensin-converting enzyme (ACE) inhibitor	Treatment of choice Reduce proteinuria and protect from progression Risk of hyperkalemia Risk of worsening renal function No adverse effects on glucose or lipid levels Avoid in renal failure
Angiotensin receptor blocker	Alternative to ACE inhibitor
Calcium-channel blocker	May use in combination with ACE inhibitor Variable effects on diabetic nephropathy
β-Blocker	No long-term data on diabetic nephropathy Increased risk of hypoglycemia May mask warning signs of hypoglycemia Use if history of myocardial infarction or tachycardia
α-Blockers	Never shown to reduce disease progression Neutral effect on proteinuria Orthostatic hypotension Neutral on lipids and glucose intolerance Recent concern about congestive heart failure

control continues to fall short of guideline-recommended levels.[159]

Existing clinical practice guidelines are not conclusive in the choice of second line antihypertensive agents. Combination therapy with agents that are tolerated and do not exacerbate existing metabolic problems are desirable.[160] Diuretics are common second line agents, because they may potentiate the effects of angiotensin blockade by overcoming the effect of sodium intake to blunt RAS blockers. In a recent clinical trial, both amlodipine and hydrochlorothiazide added to the ACEI benazepril reduced blood pressure and microalbuminuria levels.[161] β-Blockers are commonly used because of coronary artery disease and systolic dysfunction. β-Blockers may adversely affect the overall risk factor profile in patients with diabetes, whereas calcium channel blockers, ACEI, and ARBs are neutral or beneficial.[162]

Renin-Angiotensin Blockade

By the late 1980s, basic research studies identifying the importance of elevations of glomerular plasma flow, glomerular capillary pressures, and single-nephron glomerular hyperfiltration in experimental diabetes had led to the recognition that angiotensin-converting enzyme inhibition could modify the glomerular hyperfiltration and prevent the glomerular damage characteristic of the diabetic rat model.[163] The fact that other antihypertensive agents lacked these beneficial effects supported the key notion that intraglomerular hypertension was deleterious, and that ACEI and ARBs had nephroprotective effects independent of their antihypertensive properties. It should be noted that at this time neither ACEI nor ARBs are proven to reverse or stop progression of diabetic kidney disease. Several subsequent clinical trials in a spectrum of progressive renal diseases have demonstrated the benefit of ACEI in delaying progression of disease.[164] These observations were most significantly validated in type I diabetic kidney disease in the Collaborative Study Group trial with Captopril, published in 1993,[165] comparing the ACEI with placebo in patients with creatinine of less than 2.5 mg/dl and urinary protein excretion of 500 mg/day or greater. captopril slowed the progression of kidney disease by 50% and proved to reduce urinary protein excretion, despite comparable median blood pressures in the two groups. Median 24-hour urinary protein excretion was decreased by the 3-month visit in the captopril-treated group, and the reduction of almost 30% persisted throughout the study.[166] In large, randomized, controlled trials of patients with type I diabetes, ACEI diminish proteinuria and slow the progression of diabetic nephropathy[20,134] in patients with microalbuminuria and overt proteinuria. Other randomized controlled trials have suggested that reduction in proteinuria is associated with slowing of renal progression in patients with overt nephropathy. ACEI reduce the level of proteinuria more than equivalent antihypertensive doses of other classes of agents (Figure 3-10),[167] although the proteinuria advantage is lost as the systemic blood pressure declines.[65,141] A small subset of patients treated in a clinical trial setting appear to experience remission of proteinuria, and renal decline becomes nonprogressive.[168]

Analogous studies in patients with type II diabetic nephropathy have been less consistent,[101] and results are less definitive,[169–171] possibly because of small sample sizes and the use of surrogate outcomes. The clinical benefit of reducing proteinuria appears to be less significant in type II nephropathy.[172] Long-term protection was best shown in a 7-year study comparing the effects of enalapril and placebo in 94 type II normotensive patients to microalbuminuria.[169] A 5-year study period comparing the ACEI with placebo was followed by 2 additional years, during which all patients could chose enalapril or placebo. Initial ACEI therapy resulted in stable kidney function and albuminuria and reduced the risk of nephropathy by 42%; albuminuria worsened in the placebo group. Enalapril-treated patients who subsequently declined treatment noted a rise in albuminuria, whereas the placebo-treated patients who chose ACEI therapy had a reduction in albuminuria. A recent metaanalysis of ACEI in type II diabetic nephropathy indicated that ACEI produce significant reductions in proteinuria, although the effect is heterogeneous.[173] Overall, ACEI may provide similar results in type II as in type I diabetic nephropathy.

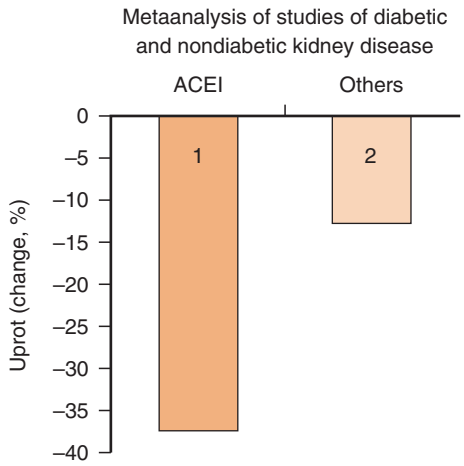


FIGURE 3-10 Effects of blood pressure-lowering agents in diabetic kidney disease. Shown are mean results for proteinuria obtained in studies that compared the effects of an ACEI with another antihypertensive agent. (Adapted from R.T. Gansevoort, W.J. Sluiter, M.H. Bemmelder, et al., Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials, Nephrol. Dial. Transplant. 10 [1995] 1963-1974.)

Relevant ACEI drug actions (Table 3-5) may include systemic and intrarenal hemodynamic effects, improvements in the filtration barrier, blockade of increased intrarenally-generated angiotensin II,[174,175] reduced interstitial expansion,[176] tissue fibrosis,[177] extracellular expansion, attenuation of diabetes-associated reduction in nephrin expression,[81,83] and restoration of tubular albumin reabsorption.[178] Systemically, increasing attention is being given to the role of tissue-based RAS and the use of blockade on other end-organ damage due to diabetes, primarily cardiovascular. ACEI slow the rise in creatinine and reduce the level of proteinuria more than equivalent doses of other classes of antihypertensive agents do, although event rates in clinical trial comparisons are similar when mean systemic pressure is less than 95 mmHg.[123] Extrarenal advantages of ACEI include lack of effects on lipid or glucose levels and more effective regression of cardiac ventricular hypertrophy.

Angiotensin II receptor blockers have effects in experimental models of diabetic kidney disease to reduce

TABLE 3-5 Differences Between the Clinical Effects of Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin II (type I) Receptor Blockers (ARBs)

EFFECT	ACE INHIBITORS	ARBs
Inhibit ACE and angiotensin-II synthesis	Yes	No
Blockade of angiotensin receptor	No	Yes
Increased plasma rennin levels	Yes	Yes
Effect on angiotensin-II formed by alternate pathways	No	Yes
Increased bradykinin levels	Yes	No
Approved for hypertension	Yes	Yes
Approved for diabetic nephropathy	Yes (captopril)	Yes
Cough, urticaria, angioedema	Yes	Less likely
Hyperkalemia	Yes	Milder
Deterioration of renal function	Potential	Potential
Contraindication in pregnancy	Yes	Yes

proteinuria, glomerular hypertrophy, and glomerulosclerosis, similar to ACEI. ARBs share many effects with ACEI (see Table 3-5) and provide a superior safety profile, including less risk of cough, angioedema, and significant hyperkalemia. In addition, ARBs may reduce urinary markers of oxidative stress in correlation with lowering albuminuria in diabetic patients.[179] Data from clinical trials have demonstrated the beneficial effects of controlling blood pressure in secondary prevention of renal progression in patients with type II diabetes.[134] Published studies have included the RENAAL study and the IDNT.[97,180–182] In the RENAAL study, losartan was compared to conventional antihypertensive therapy in 1513 patients with type II diabetes patients with diabetic nephropathy. Fewer ARB-treated patients reached the primary composite end point of doubling of serum creatinine, ESRD, or death (Table 3-6), and more achieved reduction in proteinuria. No improvement in all-cause mortality or cardiovascular morbidity and mortality occurred, although the rate of first hospitalizations for heart failure was reduced in the losartan group. A posthoc analysis indicated that proteinuria, which was reduced by losartan, was the single most powerful predictor of ESRD in the study patients.[99] Recognizing the growing population of elderly patients with diabetic CKD, a recent report addressed the safety and efficacy of ARBs in patients older than 65 years with diabetes using an age-specific subgroup analysis of the RENAAL trial results.[183] Elderly patients had the same level of benefit as younger patients, and they were not more likely to suffer adverse events such as a rise in serum creatinine or hyperkalemia. In the 27.8% of participants over age 65 years, age did not modify the efficacy of losartan in reducing the risk of the primary outcome, a composite of doubling of serum creatinine, ESRD, or death, nor of each individually. In the IDNT trial, the ARB irbesartan was compared with the calcium channel blocker amlodipine and placebo in 1715 patients with type II diabetes with hypertension and nephropathy. Risk reduction for the primary composite endpoint was reduced by irbesartan compared to either amlodipine or placebo. Two subsequent evaluations of projected survival and healthcare cost-effectiveness of irbesartan in type II diabetes and nephropathy, based on treatment-specific probabilities derived from the IDNT, have indicated that the ARB improved survival, delayed onset of ESRD by over a year, and was the least costly treatment, compared to amlodipine and control.[184,185] In both the RENAAL and IDNT studies, results were achieved in the absence of strict blood pressure control (see Table 3-6). In RENAAL, the target blood pressures (taken prior to the medication dose) of 140/90 mmHg during treatment was achieved in only 47% of losartan and 40% of placebo patients.[67] In addition, examination of RENAAL and IDNT data has indicated that 43.5% of patients taking losartan and 32.6% taking irbesartan still reached a primary end point in these studies. Results of the RENAAL and IDNT studies have led to regulatory drug approval for ARBs as initial therapy for patients with type II diabetes who are hypertensive with proteinuric renal disease. Economic evaluation of the IDNT has demonstrated the cost-effectiveness of the ARB compared to amlodipine or placebo.[182,184] The STAR study (Saitama Medical School Albuminuria Reduction in Diabetics with Valsartan) confirmed the beneficial effect of ARB therapy independent of blood pressure.[186]

TABLE 3-6 Results of ARB Clinical Trials in Type II Diabetic Kidney Disease

RESULT	IDNT (IRBESARTAN)	RENAAL (LOSARTAN)
Doubling of creatinine, ESRD, or death	20%	16%
Doubling of creatinine	33%	25%
ESRD	23%	28%
Overall death rate	NS	NS
Cardiovascular endpoints	NS	NS
First congestive heart failure hospitalization	23%	32%
Reduction in proteinuria	33%	35%

Results of ARB clinical trials in type II diabetic kidney disease. *IDNT*, Irbesartan Diabetic Nephropathy Trial; *RENAAL*, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan. (See text.) Shown are percent risk reductions for study end points and the percent reduction in proteinuria in the treatment group.
(Data from E.J. Lewis, L.G. Hunsicker, W.R. Clarke, et al., Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes, N. Engl. J. Med. 345 [2001] 851–860; and B.M. Brenner, M.E. Cooper, D. De Zeeuw, et al., Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy, N. Engl. J. Med. 345 [2001] 861-869.)

Currently, unresolved questions pertaining to RAS blockade include: When should RAS blockade be initiated? What is the optimal dosing? Is one ACEI or ARB superior to others? Are ACEI and ARBs clinically equivalent? What is the role of combination therapy?

1. Given the central role of intrarenal RAS stimulation in the pathogenesis of diabetic nephropathy, how early can RAS blockade be effective? Following the onset of diabetes in susceptible individuals, treatment of diabetic nephropathy may be primary (reduce the development of microalbuminuria), secondary (prevent the transition to overt nephropathy), or tertiary (slow the progression of established nephropathy). Secondary and tertiary interventions are now supported by clinical trial data and practice guidelines. In contrast, primary prevention to reduce the development of incident microalbuminuria in diabetes is unproven. The DIRECT trial[187] consisted of three randomized trials designed to determine whether the ARB candesartan could reduce the incidence

and progression of diabetic retinopathy compared to placebo, with negative results; data on the development of microalbuminuria were subsequently analyzed. A total of 5231 patients with normoalbuminuria were randomized. There was no statistical benefit in prevention of microalbuminuria with the ARB over a median follow-up of 4.7 years.

2. When is drug dosing optimal? Several studies have attempted to identify ways to maximize the antiproteinuric effects of RAS blockade by increasing dosages of agent used to maximum tolerated nonhypotensive doses. In a study of nondiabetic proteinuria patients, the ACEI ramipril titrated up to 20 mg/day reduced proteinuria by 29% compared to baseline, which is about three times that of conventional dosages in a comparable study.[188] However, another ACEI study showed no impact of supramaximal doses over maximal antihypertensive doses.[189] When proteinuria persists despite optimal blood pressures, changing the ACEI to ramipril or quinapril to increase tissue ACE inhibition has been suggested.[147]

3. Which ACEI or ARB is more effective? The initial regulatory trials involved comparison of losartan and irbesartan with placebo, out of a current class that includes at least five other ARBs. The AMADEO study compared two ARBs, telmisartan and losartan, over one year in patients with type II diabetes with overt nephropathy. The drugs were distinguishable in part by telmisartan's longer half-life, higher in vitro receptor affinity, and potential peroxisome proliferator-activated receptor activity. Telmisartan was more effective in reducing proteinuria (by about one quarter) without significant blood pressure differences. Although the composite endpoint of renal function and morbidity did not differ, cardiovascular and all-cause mortality appeared lower in the telmisartan group.

4. Is there clinical equivalence to ACEI and ARBs? At a time when some guidelines recommend use of ARBs as first-line therapy for type II diabetic nephropathy, the Diabetes Exposed to Telmisartan and Enalapril (DETAIL) study compared the renoprotective effects of an ARB and ACEI in equivalent doses.[190] The groups were statistically similar in the primary endpoint of decline in estimated GFR over 5 years of treatment. Albuminuria levels were highly variable and did not reach statistical separation. These results provide the longest treatment time currently available. A previously published short-term equivalence study in patients with type II diabetes also indicated no significant differences in the primary endpoint, albuminuria.[191]

The previous review indicates that both ACEI and ARBs have demonstrated favorable effects on the progression of diabetic kidney disease.[144,192] Practice guidelines developed by the American Diabetes Association, the Joint National Commission, and the National Kidney Foundation support the uses of both ACEI and ARBs in initial therapy regimens for diabetic patients. Other studies, primarily in nondiabetic patients, have indicated that the nephroprotective effects of ARBs are similar to ACEI in reducing proteinuria. The time course of reduction in blood pressure and lowering of proteinuria are concordant.[193] ACEI may be preferred in both type I and type II patients with proteinuria, but ARBs may be substituted in patients intolerant of ACEI. Although the effects of RAS blockade on mortality remain unproven, the prolongation of kidney function can be expected to improve quality of life in many cases.

5. What is the role of combination therapy? ARBs and ACEI interrupt the RAS through different mechanisms and could be synergistic in providing a higher degree of RAS blockade and renoprotection.[194,195] Theoretical advantages of combination therapy include blockade by the ARB of chymase-generated angiotensin II, lack of effect of the ARB on inhibition of kinin degradation and on aldosterone suppression, and improved receptor blockade by the ARB when AII production has been diminished.[196,197] A number of studies have attempted to confirm the theoretical benefit of combination therapy, typically in employing an ACEI and an ARB. Some data suggest that combination therapy angiotensin-receptor antagonists and ACEI at standard clinical doses is superior to maximal recommended doses of ACEI with regard to lowering blood pressure levels, with ACEI/ARB combinations leading to greater reductions in blood pressure than either class used alone.[192] Although there are no long-term studies to evaluate combination ACEI/ARB therapy to slow progression of diabetic kidney disease, several trials suggest that combination therapy is significantly more effective in reducing levels of proteinuria.[196] In 2004, Anderson and Mogensen reviewed the available combination studies in patients with diabetic nephropathy, and they reported that 5 of 10 patients showed superior proteinuria reduction with combination therapy.[198] For example, in patients with type I diabetes, dual blockade with benazepril and valsartan compared to monotherapy with each in an identical dose was compared to placebo over 8-week treatment periods. Although benazepril and valsartan were equally effective in reducing blood pressure and albuminuria, dual blockade produced an additive reduction of 43% a modest reduction in systolic and diastolic blood pressure.[128] Combination therapy was well-tolerated, consistent with previous trials alleviating concern that combination therapy might lead to more serious hyperkalemia.[195] The CALM study evaluated responses in patients with type II diabetes with Microalbuminuria. Reductions in albumin excretion were 50% with combination therapy, 39% with lisinopril, and 24% with candesartan.[199] A similar blinded short-term study in patients with type II diabetes demonstrated similar reductions in albuminuria and blood pressure with dual blockade compared to maximal doses of candesartan and an ACEI.[200] An ACEI and ARB in maximal standard doses were effective as combined therapy in a nondiabetic trial, with a safety profile no different than the ACEI alone.[201] These clinical trials supporting combination therapy in the treatment of patients with type I diabetes have been reviewed.[202] However, a clinical trial using an AT1 antagonist added to a usual maximal dose of the ACEI lisinopril did not show superior benefit to the ACEI alone, including many patients with diabetic nephropathy.[203] Alternatively, Krimholrtz reported on a 24-week trial comparing maximal ACEI therapy with either and ARB or the dihydropyridine CCB amlodipine in patinets with type I diabetes.[204] Of note, the antialbuminuric effects of the two regimens, like blood pressure reduction, were similar. In addition, the IMPROVE trial study of patients with type II diabetes with microalbuminuria, hypertension, and cardiovascular risk failed to show significant benefit of combination therapy versus monotherapy on albuminuria levels, which appeared to be more variable than anticipated in the study.[205] Finally, the ONTARGET trial of combination therapy for patients at high risk for

vascular events included over a third of patients with diabetes.[206] The combination therapy of telmisartan and ramipril did not improve cardiovascular outcomes despite a slight reduction in systolic blood pressure, and it was associated with more hypotension and syncope. Furthermore, secondary renal outcomes, reported in a subsequent paper,[207] indicated a slight increase in risk of dialysis or creatinine doubling despite better proteinuria reduction in the combination group.

Although it is reasonable to assume that increasing the extent of RAS blockade should improve the therapeutic response in diabetic nephropathy, existing studies do not adequately address the issues of drug dosing and study design, tending to compare a combination of agents to one of the agents at the same dose. The VA Nephron Study, alternatively, will compare a combination of an ACEI with an ARB with standard treatment or an ARB alone, over 5 years.[208] Finally, a metaanalysis of mostly short-term studies using combination therapy reported that combination regimens were superior to ACEI and ARBs alone in reducing proteinuria and blood pressure, with minimal deleterious effects on glomerular filtration rate and potassium levels.[209] Longer studies will be required to determine the proper role of combination ACEI/ARB therapy for diabetic CKD.[210]

Because cardiovascular disease is a leading cause of death in diabetes, particularly in patients with type II diabetes, and proteinuria is a powerful predictor of cardiovascular morbidity and mortality, cardioprotection is an important challenge in the management of patients with diabetic nephropathy. Several randomized studies of ACEI in diabetic patients with hypertension have demonstrated reductions of cardiovascular events, including HOPE and microHope,[211] CAPP,[212] and FACET.[213] However, a metaanalysis of the effects of ACEI in diabetics and nondiabetics with CKD did not reveal decreased mortality in patients with overt proteinuria treated with ACEI.[164] In the Collaborative Study Group Captopril Study,[165] the 50% reduction in risk for the combined endpoints of death, dialysis, and transplantation included only eight deaths in the captopril group and four deaths in the control group. The benefit of AT1 antagonists in reducing cardiovascular endpoints has been less consistent. Both the IDNT[151] and RENAAL studies showed no significant differences in cardiovascular, outcomes with ARB therapy, except for similar reductions in hospitalizations for congestive heart failure. However, each trial was designed to evaluate renal, not cardiovascular outcomes. The LIFE study showed more promise, with the ARB losartan more effective than conventional therapy in reducing cardiovascular morbidity and mortality in mostly patients with type II diabetes with hypertension and left ventricular hypertrophy.[214] However, there are no human data to support a cardioprotective effect independent of blood pressure when ARBs are given for renoprotection.[215] In addition, there have been no trials directly comparing ACEI and ARBs in cardioprotection of diabetic nephropathy patients. The OPTIMAL study comparing losartan and captopril in over 5000 patients with myocardial infarction reported a slightly higher cardiovascular death rate with the ARB.[216] Taking into account the results of these trials, some controversy remains regarding the selection of ACEI or ARB for cardiorenal protection in type II patients with diabetic nephropathy.[217]

EMERGING THERAPIES

Emerging therapies for diabetic kidney disease can be categorized as recently approved agents (renin inhibitors, discussed previously), drugs approved for other indications and now being evaluated in diabetic kidney disease (paricalcitol, rosiglitazone, pitavastatin), and potential new therapies (pyridoxamine, endothelin antagonists, connective tissue growth factor inhibitor, ruboxistaurin). Another drug, the glycosaminoglycan sulodexide, failed to meet study endpoints of microalbuminuria remission or reduction in its phase 3 study of patients with type II diabetes with early nephropathy in 2008.

Until recently, the main focus of vitamin D research in CKD has involved its regulation of mineral homeostasis. Its association with survival benefit in several recent clinical observational studies in stage 5 CKD has led to exploration of its mechanisms of cardiovascular effects. These include hypertension, left ventricular hypertrophy, and reduced vascular compliance. Activated vitamin D binds to the vitamin D receptor and achieves direct actions on gene expression not only in bone and intestine, but also in the kidney. Among its unique effects in the kidney are suppression of the RAS. Vitamin D suppresses renin release, and null mutant mice lacking the vitamin D receptor gene develop hypertension, hyperreninemia, cardiac hypertrophy, and more severe nephropathy.[218] Vitamin D and its analogues have demonstrable nephroprotective effects in animal studies.[219] Agarwal and colleagues evaluated the effect of the vitamin D analogue paricalcitol (19-nor-1,25-dihydroxy vitamin D2) versus placebo in predialysis CKD patients with secondary hyperparathyroidism.[220] Twice as many patients (51%) in the paricalcitol group had reductions in proteinuria. The actions of vitamin D on the RAS, the widespread use of renin-angiotensin blockade in diabetic kidney disease, and the limitations of RAS blockers due to compensatory renin release led Zhang and colleagues to investigate the value of vitamin D in a mouse model of diabetic nephropathy.[221] When added to losartan, paricalcitol resulted in more effective inhibition of the RAS and prevention of renal injury, prevention of GBM thickening, and decrease in albuminuria. The heightened effectiveness of this agent was attributed to better inhibition of the RAS. The effectiveness of paricalcitol in human diabetic CKD is being evaluated in the VITAL study. Thiazolidinediones, which are insulin-sensitizing compounds, have been associated with reduction in albuminuria in open-labeled trials of patients with diabetes, and mechanisms including inhibition of THG-β and TNF-α through PPAR-γ receptors in the kidney. In one report, 12 weeks of rosiglitazone decreased urinary albumin excretion in association with improved metabolic control.[222] Limited data have suggested that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), which have cholesterol-lowering and antiinflammatory actions, may be beneficial in diabetic kidney disease. In a mouse model, pitavastatin was recently shown to ameliorate renal mesangial expansion while reducing oxidative stress through down regulation of NOX4 expression.[223]

Based on experimental models of diabetic kidney disease, advanced glycation end products (AGEs) have been postulated to play a role in human diabetic nephropathy.[224–226] Biologically active AGEs, formed from complex nonenzymatic glycosylation reactions of proteins, lipids,

and nucleotides, can result in cross-linking between proteins, post-AGE receptor tissue effects, and altered cellular functions.[227] Several different AGE compounds have been identified in diabetic glomerulopathy lesions.[228] Toxic potential of AGEs has been described for mesangial cells, where overproduction of collagen, oxidative stress, and upregulation of insulin like growth factor, TGF, and extracellular matrix components occur, and for tubular cells, where AGE binding may lead to tubulointerstitial fibrosis. By cross-linking collagen, AGEs increase resistance to protease degradation, contributing to collagen excess and reduced urinary excretion of collagen fragments in diabetic nephropathy.[26]

Pharmacological inhibitors of AGE formation, including pimagedine[165] and pyridoxamine,[229] have been under development for several years. Pimagedine inhibits AGE formation by binding irreversibly to reactive intermediates of early glycated products.[230,231] A major phase III clinical trial of pimagedine in type I diabetic nephropathy was published in 2004.[232] In a randomized, double-blind, placebo-controlled, multicenter study, patients with established diabetic nephropathy were followed for a median of 2.5 years. Almost all were also on ACEI or ARB therapy. Both doses of the AGE inhibitor produced a statistically significant reduction in urinary protein excretion compared to placebo. In the subgroup with over two grams of proteinuria per 24 hours, doubling of serum creatinine was less likely. However, in addition to a transient flu like illness and anemia, pimagedine also produced unexpected toxicity in the form of ANCA positivity and a small number of cases of glomerulonephritis, leading to a halt in further clinical trials. A newer AGE inhibitor, pyridoxamine, is related to the natural compound, pyridoxine (Vitamin B6), and appears to have multiple activities at later stage of the AGE biosynthetic pathway by inhibiting post-Amadori activity.[233] Combined results of pyridoxamine from three phase 2 studies indicate that the AGE inhibitor reduced renal progression in type II diabetic patients with serum creatinine levels over 1.3 mg/dl.[234] A follow-up phase 2b study in patients with nephropathy due to type II diabetes is currently underway. Other AGE inhibitors are also currently being evaluated.[235]

There other new approaches to the treatment of diabetic nephropathy. These are based on an ever-growing mechanistic understanding of the causes of diabetic nephropathy where specific pathogenic roles for protein kinase C (PKC),[236] oxidative stress,[237] and TGF-β[238] have been well-established in animal models of diabetes.

PKC is comprised of a family of serine- and threonine-specific protein kinases that have been shown to play important roles in a number of physiological and pathophysiological intracellular processes.[239] Research by King,[237] Whiteside,[240,241] and others has established that activation of PKC-β and PKC-δ likely play important pathophysiological roles in the development of diabetic nephropathy. A highly specific inhibitor (LY333531) directed against PKC-β has been shown to be very effective in preventing the development of diabetic retinopathy and in slowing the development of diabetic nephropathy in animals.[242] In 1996, Ishii and colleages reported that LY333351 prevented the typical increase in glomerular filtration rate seen in diabetic rats and reduced albuminuria by 60%.[243] In 1996, Koya and colleagues studied the effect of oral PKC-β inhibition on mesangial cells from diabetic rats.[244] They found that glucose-induced increases in arachidonic acid release, prostaglandin E 2 production, and inhibition of Na-KATPase activities in cultured mesangial cells were completely prevented by the addition of LY333531. And they found that PKC-β inhibition prevented the increased mRNA expression of TGF-β1 and reduced expression of extracellular matrix components such as fibronectin and type IV collagen in the glomeruli of diabetic rats in parallel with inhibition of glomerular PKC activity. A detailed review of LY33351 and its potential may be found in review by Tuttle and Anderson.[245] Similar but even more promising results for PKC-β inhibition have been found for the prevention of diabetic retinopathy, with the Food and Drug Administration recently determining that the product could be approvable pending one additional clinical trial. Concurrent with the retinopathy trials, a pilot study of ruboxistaurin among 123 patients was completed in 2005. In a multicenter randomized prospective study, the agent was compared over one year with placebo in type II diabetic patients already stabilized on doses of an ACEI, an ARB, or both. Microalbuminuria was reduced in 24% of study patients versus 9% in the placebo group, an effect that fell just short of statistical significance.[246] Large-scale interventional trials needed to confirm the results have not been initiated at this time.

Much research has shown that increased oxidative stress is likely a critical factor in the development of diabetic nephropathy.[236] Because of this, a variety of trials of antioxidants in people and animals have been conducted. The animal studies strongly suggest that the addition of antioxidants can significantly slow development of diabetic nephropathy.[173] For example, work by Koya and colleagues have shown that heme oxygenase-1 mRNA expression, which was increased 16-fold in glomeruli of diabetic rats, had virtually no increase in animals treated with the antioxidants vitamin E or probucol.[247] Other studies in animals have shown beneficial effects for other antioxidants such as alpha lipoic acid and taurine. Some studies in small numbers of patients suggest that antioxidants may be of benefit.[248,249] Currently there are a number of studies aimed at determining whether antioxidants such as vitamin E have a therapeutic role in the treatment of diabetic nephropathy. But to date the human studies have been disappointing. It is possible that the currently available antioxidants are not effective as used. It is also possible that a better understanding of the mechanisms responsible for the increased oxidative stress will lead to the development of more targeted approaches to controlling levels of reactive oxygen species.[250] For example Recent work suggests that mitochondria are a major source of reactive oxygen species[184] and that deficiencies in intracellular antioxidants both may play major roles in the development of increased oxidative stress.[251,252] Thus therapies specifically targeted at mitigating the effects of mitochondrial oxidant production[253] and increasing specific intracellular antioxidants might provide powerful new treatments for diabetic nephropathy.

Another potential mechanism that holds much promise for therapy is inhibition of TGF-β. Diabetic nephropathy is associated with glomerulosclerosis and tubulointerstitial fibrosis. TGF-β is a protein that is presclerotic and has been strongly implicated in the pathogenesis of diabetic nephropathy. Ziyadeh and colleagues have conducted many studies

showing that high glucose upregulates TGF-β and that specific monoclonal neutralizing antibodies and antisense oligonucleotides prevent the accumulation of mesangial matrix proteins in diabetic animals.[238,254] Furthermore, long-term TGF-β inhibition in db/db mice prevented mesangial matrix expansion and preserved creatinine clearance.[255] Interestingly, there was no change in albuminuria. Because of these promising results, studies are being done to determine whether inhibition of TGF-β will help to treat progression of diabetic nephropathy in humans. Pirfenidone inhibits the actions of TGF-β and has been used to treat pulmonary fibrosis.[256] Shumar and colleagues are now using pirfenidone in an National Institutes of Health sponsored clinical trial to determine whether it can prevent worsening of diabetic nephropathy.[257]

Connective tissue growth factor (CTGF) is induced potently by TGF-β and potentiates TGF-β signaling and action. Other factors in addition to TGF-β trigger CTGF in diabetes mellitus, and CTGF is produced by multiple types of renal cells. FG-3029 is a human neutralizing anti-CTGF monoclonal antibody that competitively antagonizes the binding of TGF-β to CTGF, and it has displayed efficacy in animal models of diabetes.[258] Phase 1 studies in humans indicate a potential antialbuminuric effect of FG-3019 given intravenously in four doses over several weeks.[259]

Endothelin is released from vascular endothelial cells and is one of the most potent known vasoconstrictors. Increased endothelin production in disease states such as diabetes may produce glomerulosclerosis by promoting collagen production and podocyte injury through stimulation of endothelin A receptors.[87] Renoprotective effects of endothelin receptor blockade have been shown in preclinical studies. In experimental studies, endothelin receptor antagonists reduce diabetic renal injury,[260] in some cases independent of blood pressure. Preclinical studies in humans also support antiproteinuric effects. For example, the endothelin antagonist vasodentin reduced albuminuria in 286 patients with type II diabetic nephropathy after 12 weeks and in follow-up after 6 months.[87] The antiproteinuric effect was additive to ACEI/ARB therapy and independent of systemic blood pressure. However, significant adverse events such as fluid retention pose a potential problem and may be related to receptor nonselectivity of the endothelial antagonists under study.

At this time, there is no clear approach to complete prevention or cure for diabetic nephropathy. An intriguing, although drastic possible approach to treating diabetic kidney disease in type I diabetes is pancreas transplantation. Fioretto and colleagues studied patients up to 10 years following pancreas transplants and showed by renal biopsy that there was a clear regression of disease that was not evident 5 years posttransplant.[261] Clearly this approach cannot be widely used as the risks of immunosuppression and the relative lack of pancreases make this approach useful only in a select number of patients. Islet cell transplants may represent a safer approach to pancreas transplant in the future.

CONCLUSION

Diabetic kidney disease reflects the changing demographics of diabetes and carries an increased burden in ethnic and racial minorities. The search for biomarkers to identify those at risk for its development and progression continues. Its natural history, well-characterized, is undergoing modest revisions: many with impaired kidney function have neither microalbuminuria nor overt proteinuria, microalbuminuria does not always progress, and progression may occur unrelated to the severity of proteinuria. Cardiovascular disease frequently complicates the natural history of diabetic kidney disease. There is increasing evidence that hemodynamic and metabolic mechanisms of progression coexist and overlap, adding to the pathophysiological complexity of the disease. Inadequately treated hypertension contributes to the loss of kidney function, and effective hypertension control is the best inhibitor of disease progression. RAS blockade reduces proteinuria and has proven benefit against CKD progression, but several questions about optimal RAS blockade remain unanswered. Data on cardioprotection of ACEI/ARBs in DKD are inadequate. Potential sources of additional therapy including agents already approved for hypertension (renin inhibitors) or for other indications (thiazolidinediones, statins, vitamin D analogues), and emerging therapies (ACE inhibitors, CTGF inhibitor, endothelin antagonist).

A full list of references are available at www.expertconsult.com.

Chapter 4

HYPERTENSIVE KIDNEY DISEASE

Nitin Khosla, M.D., Rigas Kalaitzidis, M.D., and George L. Bakris, M.D.

Hypertension was the most commonly listed cause of end-stage renal disease (ESRD) until the mid-1990s. The natural history of hypertension and its impact on loss of kidney function is shown in Figure 4-1. Data from the Multiple Risk Factor Intervention Trial clearly showed a relationship between level of blood pressure and risk of developing chronic kidney disease (CKD).[1]

Since the mid-1990s, hypertension has become the second most common cause of CKD in the Western World, rivaled by diabetes.[2] This reduction in the relative importance of hypertension as a cause of ESRD is attributed to much better control of blood pressure over the past 3 decades.[3] Although it is unusual in 2009 for hypertension alone to progress to stage 5 nephropathy, hypertension is present in almost all people requiring renal replacement therapy. Epidemiological data support the notion that the prevalence of both hypertension and CKD increase with age (Figure 4-2).

In 2007, the estimated cost to treat hypertension and its comorbid conditions in the United States exceeded 69.4 billion dollars.[4] In 2006, costs for Medicare patients with CKD exceeded $49 billion, nearly five times greater than costs in 1993. Diabetes and hypertension account for about 70% of new cases of ESRD in the United States.[2] Common sense would dictate that early aggressive treatment of these comorbid conditions would increase the time to dialysis and would reduce both morbidity and cost.

One of the most difficult problems in managing patients with hypertension who also have CKD is the achievement of blood pressure targets recommended in clinical practice guidelines. Nevertheless, the degree and duration of either systolic or diastolic blood pressure (BP) elevation strongly influences cardiovascular (CV) outcomes and rate of CKD progression, even in patients with CKD. In the general population, risk of a CV event doubles for every increment of 20/10 mmHg increase in BP over 115/75 mmHg.[5] Hypertension also accelerates progression of CKD, especially when levels of proteinuria are greater than 300 mg/day.[6–10] Posthoc analyses of randomized clinical trials in patients with greater than 300 mg/day of proteinuria demonstrate that lower blood pressure levels are associated with slower CKD progression rates. These observations have lead to the development of lower BP targets, that is, to less than 130/80 mmHg, in those with CKD in an attempt to decrease the incidence of adverse CV and renal outcomes.[6,11]

This chapter reviews the following issues: 1) the pathophysiology of hypertension in CKD; 2) the association between stage of CKD and markers that predict more difficult BP control; 3) evidence supporting a lower than usual BP target in CKD, both overall and within subgroups; 4) the extent to which proteinuria should be a key element in choosing antihypertensive medications to maximally slow progression of CKD; 5) and lastly, we put forth a unified approach to achieve target BP based on recent data.

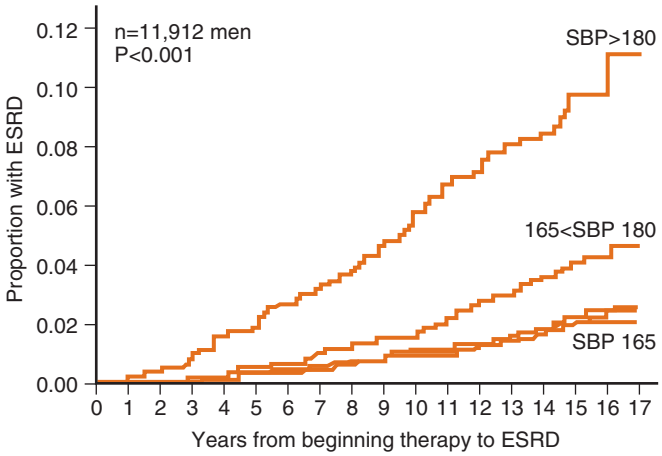


FIGURE 4-1 17-year follow-up from VA hypertension clinics on ESRD. (From H.M. Perry Jr., J.P. Miller, J.R. Fornoff, et al., Early predictors of 15-year end-stage renal disease in hypertensive patients, Hypertension 25 [1995] 587-594.)

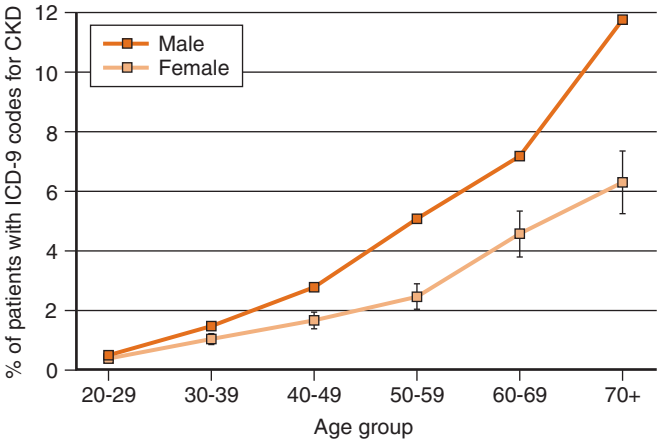


FIGURE 4-2 Percentage of patients with ICD-9 codes for CKD by sex and age, National VA 5% Sample, 2007.

PATHOPHYSIOLOGY OF HYPERTENSION IN KIDNEY DISEASE

The key components that contribute to the development of hypertension in patients with kidney disease include inappropriately elevated sympathetic nervous activity, activation of the renin-angiotensin-aldosterone system (RAAS), increased arterial stiffness, and impaired salt and water excretion by the kidney.[12,13] An increase in sympathetic activity contributes to increases in efferent arteriolar vasoconstriction (mediated through alpha-receptors), causing a greater fraction of plasma to percolate through the glomerulus and be filtered.[14–16]

This relative increase in filtration of plasma leaves a greater concentration of proteins present at entry into the network of capillaries surrounding the proximal tubule. The greater oncotic pressure (because of the protein enrichment) results in greater sodium retention.

The sympathetic nerves also stimulate renin release through activation of beta-receptors.[12,17] Release of renin ultimately results in an increase in angiotensin II. Angiotensin II increases efferent arteriolar vascular tone and increases the filtration fraction, thereby increasing the salt and protein content of plasma. Several processes other than direct sympathetic beta1-receptor stimulation also enhance renin release. As sodium absorption in the proximal renal tubule increases, the amount of sodium present in the distal parts of the nephron diminishes. This fall in distal nephron sodium concentration serves as an additional stimulus for renin release. Afferent arteriole stretch also falls as kidney perfusion diminishes in the face of a falling cardiac output, and this fall in afferent arteriolar tone represents another renin-release signal.

In addition to effects on efferent arteriolar tone, angiotensin II also stimulates proximal tubule cells to recover directly filtered sodium through enhancement of activity in the Na/H antiporter on the luminal side of the epithelial cell. Angiotensin II is a potent stimulus to aldosterone production and release, and angiotensin II indirectly stimulates distal tubule sodium recovery by stimulating aldosterone release, which primary acts to resorb sodium at this distal site.

Aldosterone is produced and released under several circumstances. Angiotensin-II, and to a lesser extent, adenocorticotropin hormone (ACTH) from the pituitary gland, regulate aldosterone production and release; increases and decreases in potassium intake also increase aldosterone production and release. Aldosterone stimulates the activity of the sodium-potassium adenosine triphosphate-ase (ATPase) enzyme on the basolateral side of epithelium and thereby prompts transporting epithelial cells, like those in the distal nephron and the cortical collecting duct of the kidney, to increase sodium reabsorption. As aldosterone increases sodium uptake into cells, potassium or hydrogen ions are extruded into the urinary lumen to replace the recovered sodium and balance the residual negative charges, which in turn leads to hypokalemia and alkalosis.

As kidney disease progresses, the ability of the kidney to excrete salt and water deteriorates. Overactivity of the sympathetic nervous system results in activation of the RAAS, which also impairs the ability of the kidney to excrete salt and water. Multiple other physiological factors may play a role in impaired salt and water excretion including insulin resistance, altered endothelin function, reduction of nitric oxide synthesis, and altered prostaglandin production. The resultant increase in extracellular volume plays a role in the exacerbation of high BP in kidney disease.

Several nonhemodynamic effects of angiotensin II also contribute to kidney disease. Angiotensin II stimulates mesangial cell proliferation, induces expression of transforming growth factor-β, and stimulates production of plasminogen activator inhibitor-1. All of these factors may mediate renal inflammation and glomerular and tubulointerstitial fibrosis.[18]

Increased arterial stiffness also plays a role in hypertension in kidney disease.[19–21] This can be mediated by both vasoconstriction and the inability to vasodilate through complex neurohumoral and metabolic mediators. Factors that lead to excess vasoconstriction include overactivity of the sympathetic nervous system, activation of the RAAS, and smooth muscle hypertrophy mediated by angiotensin-II and potent vasoconstrictors including endothelin. Impaired vasodilation often occurs as a result of endothelial dysfunction and prostaglandin deficiency.

Lastly, the genetic contribution to hypertension and kidney disease is clear and much work has occurred over the past decade to help clarify the genes involved. Recent

developments in this area have identified a strong association between genetic variants in the gene that encodes the molecular motor protein nonmuscle myosin 2A (*MYH9*) and ESRD in African Americans without diabetes.[22] These new data demonstrate that much of the excess risk of ESRD in African American individuals is attributable to an *MYH9* risk haplotype and suggest that hypertension may cause progressive kidney disease only in genetically susceptible individuals. These findings also raise the question of whether in some cases of hypertensive renal disease, hypertension may be the result rather than the cause of a primary underlying renal disease.[22,23]

Polymorphisms of a different candidate gene, important for sympathetic nervous system function and related to hypertension, are also associated with hypertensive nephrosclerosis in some African American patients.[24] *CHGA* gene polymorphisms are associated with hypertensive nephrosclerosis in African Americans.[22] Moreover, a common variant C+87T in the *CHGA* 3'-UTR is a functional polymorphism causally associated with hypertension, especially in men in the U.S. population.[25] Thus, *CHGA* clearly contributes to hypertensive nephrosclerosis in a subset of patients with CKD. Taken together, these data provide optimism that a family of genes can be identified to predict future risk of kidney disease or hypertension in certain cohorts.

ASSOCIATION OF CHRONIC KIDNEY DISEASE STAGE AND LEVEL OF BLOOD PRESSURE CONTROL

It well known that patients with stage 3 or higher CKD have a much greater prevalence of resistant hypertension.[3] Resistant hypertension is said to be present when a patient has a blood pressure above 140/90 mmHg[26] and is on maximal doses of three different antihypertensive agents with complementary mechanisms. In addition to low glomerular filtration rate (GFR), the most common risk factors for resistant hypertension include obesity, failure to reduce sodium intake, and the presence of microalbuminuria (MAU).

MAU defined as an albumin excretion of greater than 30 to 299 mg/day or 20 to 200 μg/min that is present on two different occasions.[27] MAU is a marker of endothelial dysfunction and is an independent risk marker for CV events.[28–31] It is not a marker of kidney disease[32] as previously thought. Increases in MAU over time, however, are markers of worsening endothelial function, which is associated with worsening kidney function because the kidney is one of the most vascular organs in the body.

Measurement of MAU with a simple spot urine can provide as much if not more information as other inflammatory markers such as high sensitivity C-reactive protein.[27] The best evidence demonstrating the association between MAU reduction and reduction in CV events comes from a posthoc analysis of the Losartan Intervention for Endpoint trial, where an early reduction in MAU was associated with a greater reduction in CV events that persisted over the 5-year follow-up.[33] Studies also demonstrate that in patients with diabetes and very early stage 2 CKD, the presence of MAU required, on average, one additional antihypertensive medication to achieve BP goal.[34]

Macroalbuminuria, also referred to as proteinuria, is defined as a protein excretion rate greater than 300 mg/day or greater than 200 μg/min.[35] It is associated with a higher CV risk than microalbuminuria and does indicate presence of CKD; there is a direct relationship between the magnitude of proteinuria and progression to ESRD.[36] Posthoc analyses of four appropriately powered CKD outcome trials demonstrate that reduction in macroalbuminuria (proteinuria) in those with advanced CKD delays CKD progression, an effect that could not be explained by BP lowering alone.[37] These studies demonstrate a reduction in proteinuria of more than 30% from when treatment started result in a 39% to 72% risk reduction for dialysis at 3 to 5 years (Table 4-1).[37–39]

Given this information, there have been numerous attempts to have the Food and Drug Administration approve changes in albuminuria as a surrogate marker for CKD progression. This effort has failed because the there is no randomized prospective trial that demonstrates that a change in albuminuria alters CKD progression independent of BP reduction. Hence, albuminuria does not qualify as a surrogate marker as it has not been implicated as contributing to the pathophysiology of CKD progression.[40,41]

TABLE 4-1 Outcomes Studies with Primary CKD Progression Endpoint

STUDY	TREATMENT GROUPS	FOLLOW-UP (MEAN IN YEARS)	ACHIEVED BLOOD PRESSURE (mmHg)	CHANGE IN PROTEINURIA	RELEVANT OUTCOMES
Captopril trial	Captopril or placebo	3 (median)	MAP 96 MAP 100	−30%	Captopril delayed the progression of diabetic nephropathy.
AASK*	Metoprolol, ramipril, or amlodipine and conventional or intensive blood pressure targets	4	128/78 for lower group 141/85 for usual group	−14% for metoprolol −20% for ramipril +58% for amlodipine at 6 months	Ramipril slowed the progression of renal disease when compared to the other groups.
RENAAL*	Losartan or placebo	3.4	140/74 142/74	−35%	Losartan delayed the need for dialysis by 2 years when compared to placebo.
IDNT*	Irbesartan or amlodipine or placebo	2.6	140/77 141/77 144/80	−33% −6% −10%	Irbesartan reduced proteinuria to a greater extent and lead to slower progression of renal disease when compared to the other groups.

*Indicates studies where posthoc analysis shows significant risk reduction for CKD progression when proteinuria reduced by more than 30% at 6 months; MAP, mean arterial pressure.

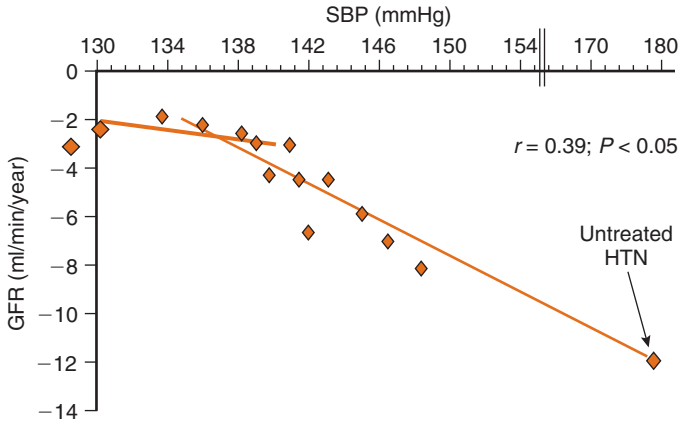


FIGURE 4-3 The relationship between achieved level of BP and rate of decline in renal function in renal outcome trials over the past decade. (From P.A. Sarafidis, G.L. Bakris, Kidney disease and hypertension, in G. Lip, J.E. Hall [Eds.], Comprehensive Hypertension, first edition, Mosby, London, 2007, pp 607-620.)

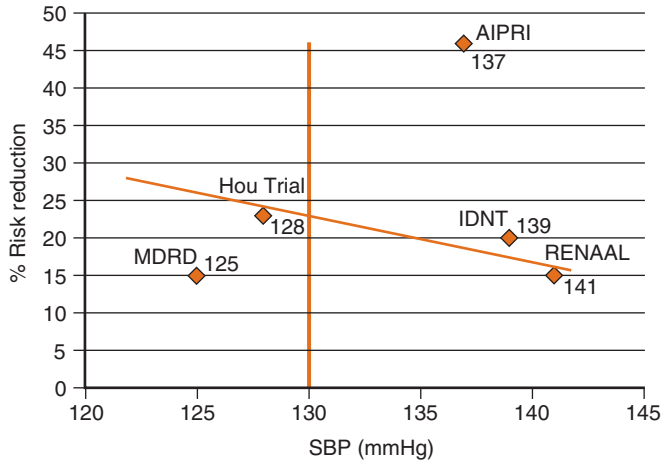


FIGURE 4-4 Achieved systolic BP in all prospective randomized CKD outcome trials.

Lastly, baseline kidney function and level of protein excretion are also key determinants of outcomes in CKD trials. The earlier in the course of CKD a BP intervention occurs, the more likely this intervention is to slow or halt progression. For example, in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial and the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) CKD progression (defined by change in creatinine clearance in the ABCD trial and development of MAU in the BENDICT trial[42]) was normalized. In The ABCD trial, the average GFR was more than 80 ml/min/1.73 m^2 at the start of the trial, whereas in most other diabetes trials, baseline GFR is generally less than 50 ml/min/1.73 m^2 at baseline.[43] Early and aggressive BP lowering to less than 130/80 mmHg in the ABCD trial slowed loss of GFR to rates seen in people with normal kidney function. Conversely, in other trials of more advanced CKD, GFR loss occurred at a rate of 2 to 7 ml/min/year, as seen in Figure 4-3.[11,44] Thus, results of trials in patients with advanced proteinuric CKD should not be extrapolated to patients with early CKD, because rates of decline in kidney function are not similar.

TABLE 4-2 Summary of Guidelines and Position Papers for Goal Blood Pressure in People with Kidney Disease or Diabetes from Various Consensus Committees around the World

GROUP	GOAL BP (mmHg)	INITIAL THERAPY
American Diabetes Assoc. (2009)	<130/80	**ACE Inhibitor/ARB*#**
Am. Society of HTN (2008)	≤130/80	**ACE Inhibitor/ARB**
National Kidney Foundation. (2007)	<130/80	**ACE Inhibitor/ARB***
Japanese HTN Society (2006)	≤130/80	**ARB*#**
National Kidney Foundation (2004)	<130/80	**ACE Inhibitor/ARB***
British HTN Society (2004)	≤130/80	**ACE Inhibitor/ARB**
JNC 7 (2003)	<130/80	**ACE Inhibitor/ARB***
ISH/ESC (2003)	<130/80	**ACE Inhibitor/ARB**
Australia-New Zealand (2002)	<130/85	**ACE Inhibitor**
WHO/ISH (1999)	<130/85	**ACE Inhibitor**

*Indicates potential use of initial combination therapy with a thiazide diuretic, if BP substantially higher than goal.
#Indicates calcium antagonists could also be combined.

SHOULD ALL PATIENTS WITH CHRONIC KIDNEY DISEASE HAVE A BP GOAL OF LESS THAN 130/80 mmHg?

All published guidelines define goal BP as less than 130/80 for those with diabetes or CKD (Table 4-2).[6,11] Data to support the goal of less than 130/80 mmHg among those with diabetic nephropathy come from posthoc analyses of three different trials of patients with advanced (estimated GFR [eGFR] <60 ml/min/1.73 m^2) proteinuric (>300 mg/day) kidney disease. Mean achieved systolic and diastolic blood pressures at trial completion are shown in figure 4.4. The relationship between level of BP reduction and risk of cardiovascular events was J-shaped rather than linear, suggesting that a BP below a systolic pressure of 120 mmHg may actually increase cardiovascular risk in these patients.[45] Thus, even in diabetic nephropathy where the data are somewhat more robust, the argument for a BP less than 130/80 mmHg is weak.

Nondiabetic CKD trials are even less robust with regard to BP goal, as only two such trials randomized to different levels of BP, the Modification of Diet in Renal Disease Study (MDRD) and the African American Study of Kidney Disease (AASK). Like those in patients with diabetic nephropathy, these trials were conducted in patients with an eGFR less than 60 ml/min/1.73 m^2 who had macroalbuminuria.

The MDRD provides randomized participants to two levels of BP and followed them for progression of nephropathy (mean arterial pressure [MAP] <92 mmHg versus 102 to 107 mmHg). When the trial ended after 2.7 years, progression was no different between the two groups. However, after 8 additional years of follow-up, those with baseline proteinuria of more than 1 gm/day randomized to the lower target BP of 92 mmHg had a slower decline in kidney

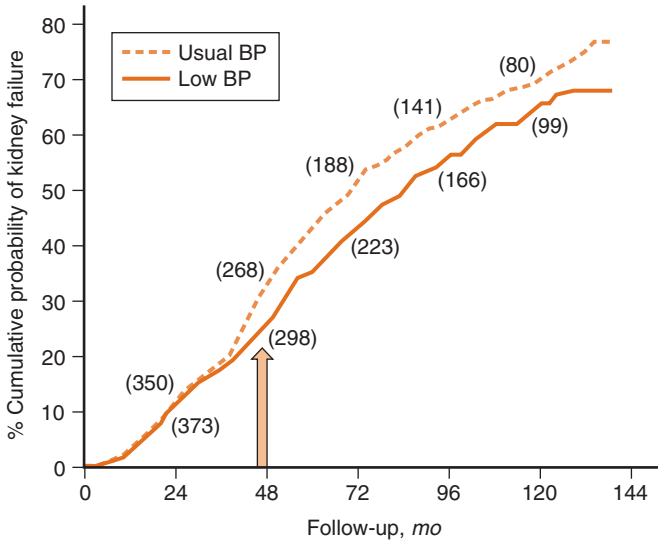


FIGURE 4-5 Cumulative probability of kidney failure following 12 years of follow-up in the MDRD trial. (From M.J. Sarnak, T. Greene, X. Wang, et al., The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study, Ann. Intern. Med. 142 [2005] 342-351.)

function and a lower incidence of renal failure compared to those randomized to a MAP of 107 mmHg.[46] This difference was apparent within 1 year after the study ended (Figure 4-5).

The AASK study adds support to the notion that patients with significant proteinuria benefit from a lower BP target. The primary analysis of AASK demonstrated that patients randomized to a MAP of less than 92 mmHg derived no additional benefit on CKD slowing compared with those randomized to a MAP between 102–107 mmHg. However, a subgroup analysis among 52 patients with proteinuria greater than 1 g/d showed that the lower BP target demonstrated a slight trend toward preservation of kidney function (Figure 4-6).[47]

Many cite the Ramipril Efficacy in Nephropathy (REIN-2) trial as evidence to refute the notion that lower BP targets slow progression in patients with advanced nephropathy and proteinuria.[48] However, this study was grossly underpowered to detect a difference in decline in GFR between the two BP groups as the median follow-up was only 1.6 years and there was only a 4.8 mmHg difference in systolic BP difference between treatment groups. Note this is the same level of difference seen in the Hypertension Optimal Treatment (HOT) trial that failed to show a difference in cardiovascular outcomes.[49] Also note that all the trials arguing for a lower BP target in CKD are limited because the data presented to support the argument are derived from posthoc analyses.

Perhaps the supportive evidence to reevaluate the goal BP in CKD patients comes from the latest 10-year follow-up of the AASK trial. Participants in this trial were followed for an additional 5 years after completion of the trial and had systolic BP levels averaging less than 135 mmHg in the entire cohort.[50] Even with this level of control, about 65% of the cohort still experienced progression, albeit markedly slowed, of the presence of masked and nocturnal hypertension that was missed by routine BP measurement. This may explain continued progression despite achievement of blood pressure targets on office visits.[51] Taken together, these data support the following: a) routine BP measurements are not adequate for determining risk of CKD progression in patients with preexisting CKD; b) the goal BP of less than 130/80 mmHg in CKD is not supported by appropriately powered trials in CKD but comes from meta analyses of smaller trials and posthoc analyses of larger trial databases.[11,52] Lastly, limited evidence does support a goal of less than 130/80 mmHg in the subgroup of patients with macroalbuminuria or proteinuria and CKD. Although the long-term follow-up of MDRD showed a benefit to lower BP targets among those with high levels of proteinuria, this difference was not reproduced in long-term follow-up of AASK participants.[50] One of the hypotheses put forth as to why the AASK participants did not derive a benefit was the lack of true 24-hour BP control because two-thirds had either masked hypertension or no nocturnal drop in BP.[51–53]

These data taken together suggest that in patients with baseline GFR values less than 50 ml/min/1.73 m^2 and proteinuria, those with BPs that approach 130/80 mmHg have slower rates of decline in kidney function. Additionally, the AASK experience provides a rationale for performing 24-hour ambulatory blood pressure monitor (ABPM) periodically to ensure BP control over the 24-hour period.

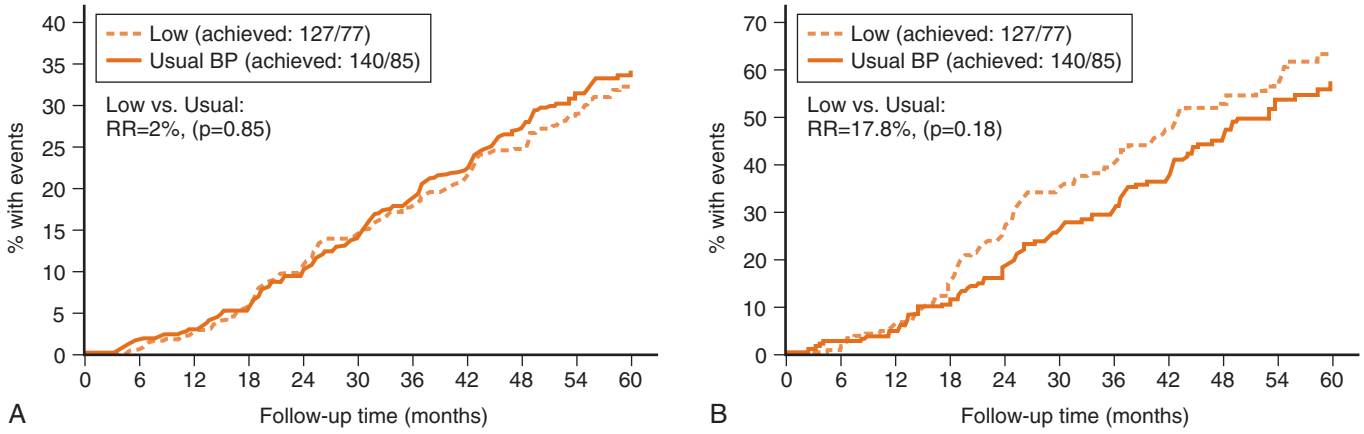


FIGURE 4-6 **A,** Main AASK trial outcome of composite clinical events including declining GFR, ESRD, and death. RR, risk reduction. **B,** AASK subset of patients with baseline urine protein: creatinine greater than 0.22 (>300 mg/day) randomized to different BPs. (From J.T. Wright Jr., G. Bakris, T. Greene, et al., Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial, JAMA 288 [2002] 2421-2431.)

PROTEINURIA REDUCTION AND CHRONIC KIDNEY DISEASE PROGRESSION: SHOULD IT BE CONSIDERED?

Proteinuria or macroalbuminuria (>300 mg/d) is *not* an approved surrogate marker for CKD progression by the Food and Drug Administration. The major reason for this stance is that a BP-independent effect of proteinuria on progression of CKD has not been convincingly demonstrated. Thus, changes in proteinuria probably reflect either the direct effect of BP reduction or improvement in podocyte function as a result of better BP control. Nevertheless, the data are clear that development of proteinuria (>300 mg/day) despite adequate BP control is a clue that CKD is present and progressing. Proteinuria greater than 2.5 grams per day is an uncommon consequence of hypertension in the absence of diabetes and should prompt consideration of a renal biopsy to determine the etiology of renal disease.

Posthoc analyses of all studies, to date, demonstrate that maximal slowing of nephropathy occurs only when proteinuria is reduced in concert with BP.[53] Proteinuria reduction of at least 30% below the average initial measurement should occur after 6 months of BP lowering treatment (see Table 4-1).[7] Note, however, that this is not true for patients with CKD and microalbuminuria. There is no randomized trial with proteinuria reduction as a primary endpoint linked to nephropathy progression.[27,53] Nevertheless, the totality of the data argues for a strategy that lowers both proteinuria and BP to maximally reduce nephropathy progression.[53,54]

THERAPEUTIC APPROACHES TO HYPERTENSION IN KIDNEY DISEASE

The approach to BP control in patients with nephropathy has to be viewed not only in the context of the current guidelines but also in the context of data that have not yet made it into guidelines. Specifically, in patients with advanced proteinuric nephropathy, that is, those with a GFR less than 60 ml/min/1.73 m^2 and greater than 300 mg/day of proteinuria, the strategy to maximally reduce nephropathy progression should ensure the following: a) adequate 24-hour BP control, b) at least a 30% reduction in proteinuria from when treatment started, and c) and use of agents that inhibit the RAAS.

The lifestyle approaches to treating BP in those with early CKD have not changed since published in 2004 National Kidney Foundation guidelines.[6,11] The available data, however, suggest that lifestyle modifications alone are inadequate for management of hypertension in patients with stage 2 or higher CKD.[6,11]

There are a few aspects of lifestyle management, however, that need emphasis. First, is *sodium restriction*. High sodium intake is particularly injurious in people who are black because they excrete a lower sodium load than their white counterparts.[55] This difference of renal sodium handling is borne out by the results of the Dietary Approaches to Stop Hypertension (DASH) trial, where hypertensive black females had a 6 mmHg greater reduction in BP compared to hypertensive white females on a low sodium, high potassium diet.[56] The DASH diet should be prescribed with caution, if at all, in anyone with stage 4 or higher nephropathy because of risk of hyperkalemia.

Those with CKD are sodium avid, a phenomenon that is amplified in those with diabetes or metabolic syndrome because the high levels of insulin seen in these conditions affect the tubular reabsorption of sodium.[57–60] Hence, those who are obese or have diabetes are relatively volume expanded.[61] Ingesting high sodium loads blunts the antiproteinuric effects of RAAS blockers.[62–64] Therefore, limitation of daily sodium intake to 2 to 3 gm/day is a logical initial therapeutic approach with use of a thiazide diuretic in those with a GFR greater than 50 ml/min/1.73 m^2 who do not fully adhere to this recommendation.

Pharmacological Therapy

Both the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the National Kidney Foundation (NKF) state that management of hypertension in CKD should focus on reducing BP with the NKF also emphasizing reducing protein excretion. Initial treatment with renin angiotensin-aldosterone system (RAAS) blockers such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)[6,11] is recommended usually in concert with either diuretics or calcium antagonists to achieve BP targets. The American Society of Hypertension has recently updated the existing BP guidelines for the treatment of diabetic nephropathy in a position paper. The algorithm summarized in the paper is shown in Figure 4-7.[6,11,65]

RATIONALE FOR USE OF CERTAIN DRUG CLASSES

Blockers of the Renin-Angiotensin-Aldosterone System

The RAAS blockers are generally avoided by most physicians in the patients who would garner the greatest benefit, specifically those with an eGFR less than 50 ml/min/1.73 m^2 with proteinuria.[66] Although the people in the clinical trials are those with an average GFR of 35 to 40 ml/min/1.73 m^2 with more than 500 mg/day of proteinuria, these are the exact patients in whom RAAS blockers are often avoided because of increases in creatinine or fear of hyperkalemia. These were problems seen in the trials, but they rarely required discontinuation of RAS blockers. Furthermore, a rise in serum creatinine among such patients actually is associated with better CKD outcomes.[67] Moreover, this recommendation is in all CKD guideline statements.

Angiotensin-Converting Enzyme Inhibitors

The mechanism of kidney protection from blockers of the RAAS relates to many factors including hemodynamic and antifibrotic effects and effects on renal reserve. The nephron responds to a variety of factors, such as increased protein intake, with an elevation in GFR. This is referred to as renal reserve because it reflects the ability of the kidney to increase its clearance rate in the presence of higher urea genesis.[68] The increase in GFR is due to signaling from the macula densa to the afferent glomerular arterioles resulting in a

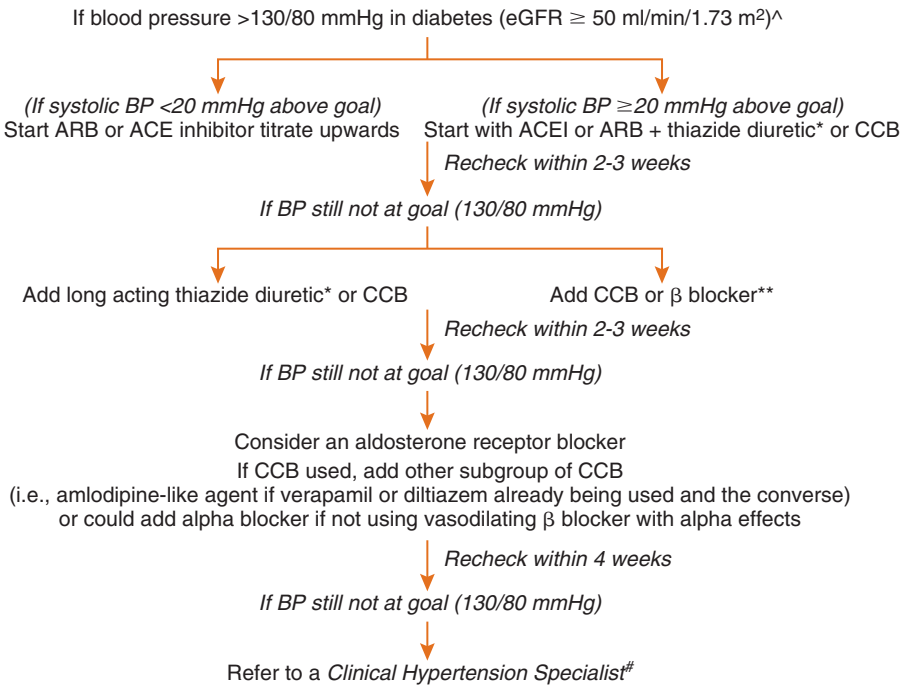


FIGURE 4-7 An approach to lower arterial pressure to goal in patients with diabetes and/or albuminuria. It represents a position paper of the American Society of Hypertension updated from the JNC 7. (From G.L. Bakris, J.R. Sowers, ASH position paper: treatment of hypertension in patients with diabetes-an update, J. Clin. Hypertens. [Greenwich] 10 [2008] 707-713.)
^Represents kidney function (estimated glomerular filtration rate-eGFR) that generally responds well to thiazide diuretics.
*Chlorthalidone is the suggested thiazide like diuretic since this is the diuretic used in clinical trials and forms the bases for the cardiovascular outcome data.
**Vasodilating beta blockers have a better tolerability profile and less metabolic consequences as compared to older agents such as atenolol.
#Specialists can be found at http://www.ash-us.org/specialist_program/directory.htm#

vasodilator response to various amino acids. ACE inhibitors blunt the rise in GFR that follows a protein load by blocking this afferent arterial dilation.[69] Thus, agents that block the RAAS protect the kidney in a manner similar to the way β-blockers provide cardioprotection.

The first trial to demonstrate a benefit of ACE inhibitors was the Captopril Nephropathy Trial in type I diabetics. This trial demonstrated an almost 75% risk reduction in doubling of serum creatinine and in the combined outcomes of death, dialysis, and kidney transplantation in those treated with captopril when compared to placebo in those whose serum creatinine values were greater than 2.0 mg/dl. In those with serum creatinine values of less than 1.0 mg/dl, there was no significant benefit to ACE inhibition when similar BPs where achieved.[70] The Ramipril Efficacy in Nephropathy (REIN) trial also demonstrated a 62% reduction in renal disease progression in those with serum creatinine values greater than 2.0 mg/dl and greater than 3.0 g/day proteinuria, compared to a 22% reduction in those with MAU alone.[71] Similar findings were noted in meta analyses of nondiabetic renal disease.[52]

Early clinical trial data suggested that ACE inhibitors may provide additional protection against nephropathy progression, independent of BP, but this has not been borne out in larger clinical trials.[52,72] In a posthoc analysis of the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), there was no evidence favoring the concept that ACE inhibitors have unique effects, independent of BP control, on preservation of renal function.[72] This difference in CKD outcomes among these trials relates to several factors. In earlier studies, all patients had advanced CKD, that is, a GFR less than 50 ml/min/1.73 m^2 with more than 500 mg/day proteinuria. The ALLHAT was not powered for CKD outcomes and had no proteinuria data. Moreover, it had very few people with stage 3 or 4 nephropathy. Another factor was that within the first 2 years of ALLHAT, as much 6 mmHg difference in systolic BP existed between the ACE inhibitor group and the diuretic group. Consequently, the observed lack of selective benefit of ACE inhibitor treatment is difficult to interpret.

As previously mentioned, increases in serum creatinine are commonly seen within a few weeks of starting ACE inhibitors or ARBs, especially in those with advanced nephropathy. A rise in serum creatinine limited to 30% to 35% within the first 4 months of starting RAAS-blocking therapy, however, correlates with preservation of kidney function over a mean follow-up period of 3 or more years (Figure 4-8).[11,67] This correlation between a limited early rise in serum creatinine and long-term preservation of kidney function was restricted to patients younger than 66 years old with baseline serum creatinine values of 3.5 mg/dl or less. If acute increases in serum creatinine of greater than 40% occur in less than 4 months of RAAS blocker therapy, then the physician should evaluate the patient for: 1) volume depletion (the most common etiology), 2) worsened heart failure, or 3) bilateral renal artery stenosis.[67] Elevations in serum potassium only become clinically relevant at levels markedly above 6 mEq/L or 5 mEq/L in the presence of digitalis preparations. Data from the heart failure trial demonstrated a CV risk reduction in people with CKD with serum potassium levels up to 5.7 mEq/L.[73] Hyperkalemia can be addressed

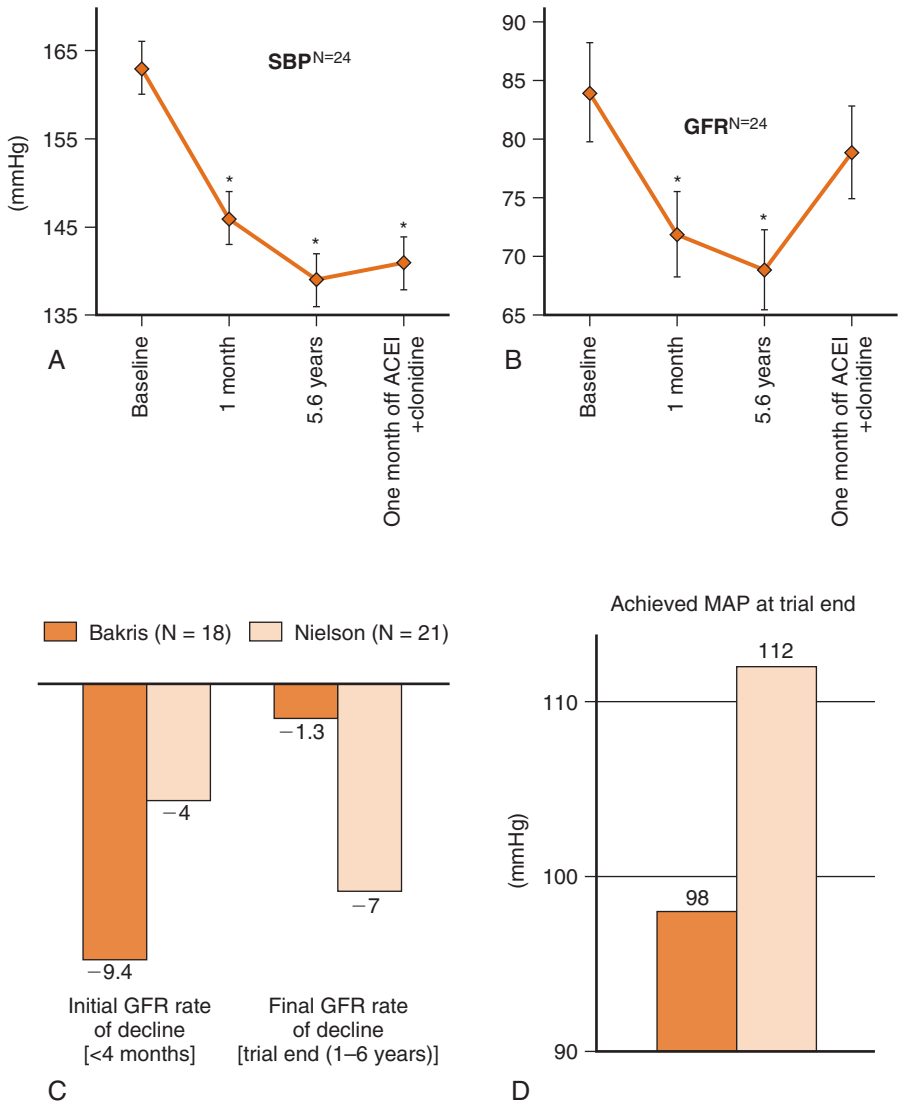


FIGURE 4-8 Initial and long-term change in glomerular filtration rate (GFR) in patients with type 2 diabetes initially started on the ACE inhibitor, lisinopril. Note GFR was measured using ^{99}Tc-DTPA. Patient baseline characteristics were similar in both studies. Note with better BP reduction the GFR dropped more initially in study, but the overall rate of decline at 5 years was less in the group with better BP control in spite of a greater initial fall. (From G.L. Bakris, M.R. Weir, Angiotensin-converting enzyme inhibitor associated elevations in serum creatinine: is this a cause for concern? Arch. Intern. Med. 160 [2000] 685-693.)

by advising on avoidance of high potassium foods such as fruits and vegetables, appropriately dosing diuretics, and stopping agents known to increase potassium, such as nonsteroidal antiinflammatory agents. An approach to manage changes in serum creatinine from RAAS blockers is offered in Figure 4-9.[67]

Angiotensin II Receptor Blockers

The Reduction of Endpoints in NDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan in Diabetic Nephropathy Trial (IDNT) demonstrated that in advanced nephropathy, using an ARB to reduce BP led to a decrease in rate of nephropathy progression greater than that seen with other agents, for example, amlodipine or beta blockers/diuretics.[74,75] The primary composite endpoint for both studies was time to doubling of baseline serum creatinine, onset of ESRD, or death. In the RENAAL study of 1513 patients who were followed for an average of 3.4 years, and the IDNT of 1715 patients who were followed for an average of 2.7 years, there was a 16% and 37% risk reduction by losartan and irbesartan, respectively, for the primary endpoint. In the RENAAL trial, there was a 28% increase in time to ESRD. It was estimated that losartan could delay the need for dialysis or transplantation for 2 years.[74] Taken together, these trials reinforce the importance of selecting agents that both help achieve BP goal and reduce proteinuria (see Table 4-1).

Data directly comparing renal outcomes of ARBs and ACE inhibitors are limited to one trial that was underpowered and not in a cohort that would yield a meaningful outcome on CKD progression; hence, there is no difference between the two classes.[76] The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin Converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial also compared these classes and their combined use on CKD progression, but major data inconsistencies preclude its credibility; hence, the trial is not discussed.[77] Another trial, however, that evaluated use of either an ACE inhibitor or an ARB alone or together was The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).[78] This trial was powered for cardiovascular outcomes in high-risk patients and failed to show a benefit

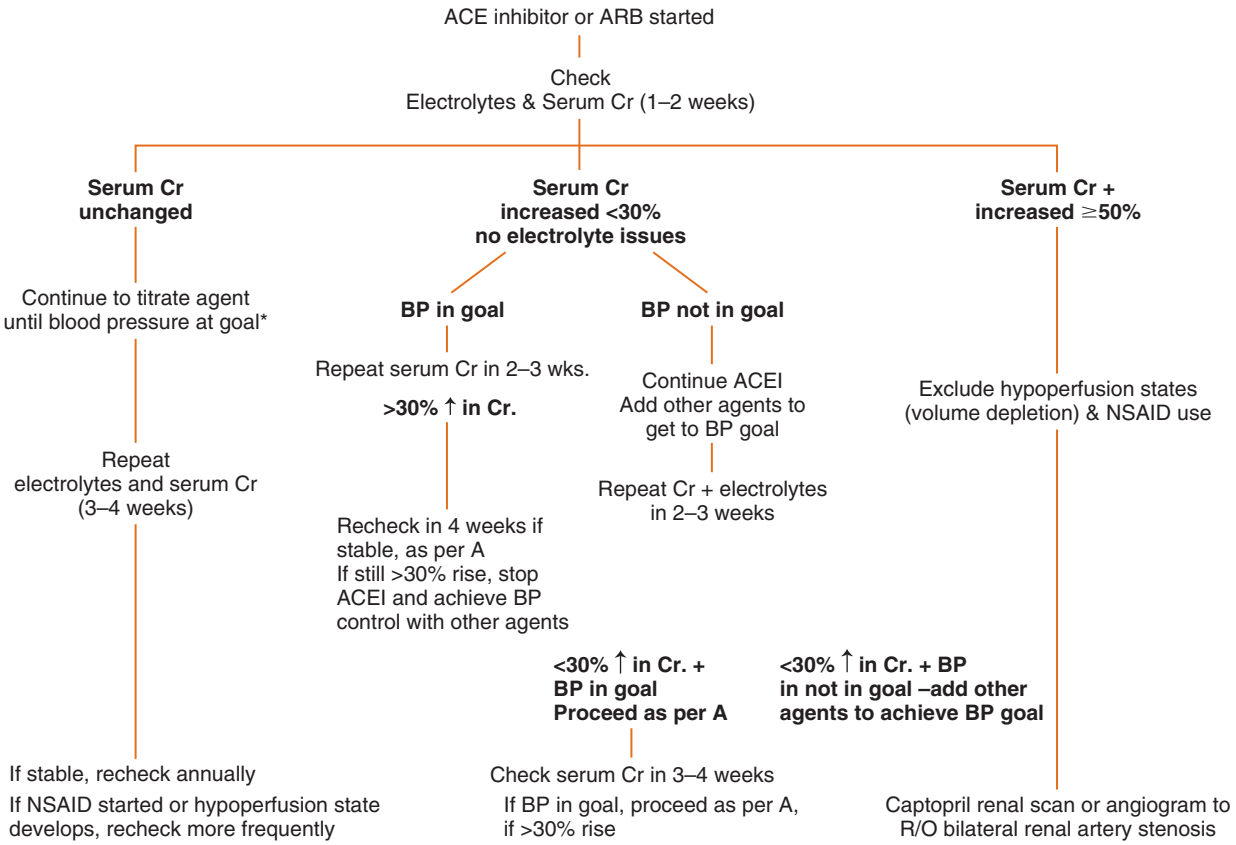


FIGURE 4-9 An approach to management of elevated serum creatinine secondary to RAAS blockade. (From G.L. Bakris, M.R. Weir, Angiotensin-converting enzyme inhibitor associated elevations in serum creatinine: is this a cause for concern? Arch. Intern. Med. 160 [2000] 685-693.)
*BP as per current guideline goals for kidney disease.
**Reduce ACEI or ARB by 50% and add another drug that has a complimentary mechanism. If this increase in creatinine occurs within the first month strongly consider hypoperfusion or NSAIDs.

of the ACE inhibitor/ARB combination over either agent alone. Moreover, it showed a higher risk of hyperkalemia with use of the combination. A posthoc analysis of the trial also evaluated CKD progression assessed by change in creatinine over time.[79] This trial does not answer the question about progression of CKD progression in patients with advanced nephropathy, because few patients with advanced nephropathy were included.[80] Moreover, the interpretation that the group receiving a combination regimen had more renal events was troubling, because it was driven by the number of acute dialysis events for hyperkalemia. Most of the people who received acute dialysis required one or two treatments, and none required chronic dialysis. Moreover, the loss of eGFR in the combination group was 6 ml/min/1.73 m^2 over 56 months or 1.2 ml/min/year, clearly within the normal range of GFR loss over time.[80] Thus, to date, there are no clear data to support use of combined RAAS blockade to slow nephropathy progression further. Their combined use, however, to lower albuminuria among those with more than 300 mg/day is clear.[81,82] The results on an ongoing Veteran's Administration randomized clinical trial may answer the question as to whether RAAS combination further slows nephropathy progression, but the results are more than 2 years away.

In general, ARBs are generally better tolerated than ACE inhibitors because they are associated with a lower incidence of cough (presumably because they do not affect bradykinin), angioedema, taste disturbances, and hyperkalemia.[78,83] In the ONTARGET the angioedema rates were higher in the ramipril group (0.1% telmisartan vs. 0.3% ramipril, P = 0.01) with a threefold higher incidence of cough in the ramipril group 4.2% versus 1.1% in the telmisartan group.[78]

Direct Renin Inhibitors

Aliskiren is the first and only approved direct renin inhibitor. The mechanism of action of this drug is unique in that it blocks the RAAS by binding to a pocket in renin itself, preventing it from cleaving angiotensinogen to angiotensin I. Aliskiren has a half-life of 24 hours and a side effect profile that is similar to that of ARBs.[84] The role for aliskiren in the management of hypertension has yet to be fully determined, but it effectively reduces BP when used alone or in combination with other classes of medications such as diuretics, ARBs, and calcium channel blockers (CCBs).[85]

Limited data are available describing the use of aliskiren in CKD patients. The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study compared the effect of aliskiren combined with losartan and losartan combined with placebo on albumin excretion in 599 patients with diabetes. Both groups had similar BPs, and the aliskiren group had a 20% reduction in urinary albumin-to-creatinine ratios when compared to

the placebo group at 6 months.[86] Although these results are promising, we must await the results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial to see if the effects are similar to that of ACE inhibitors and ARBs on diabetic nephropathy progression.

Aldosterone Antagonists

Current recommendations are to use aldosterone antagonists for treating hypertension in patients with advanced heart failure and following myocardial infarction.[6] However, the role of these medications continues to expand. A posthoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) demonstrated that adding spironolactone as fourth-line therapy led to a dramatic 21.9/10.5 mmHg reduction in BP.[87] Others have looked at using aldosterone antagonists as a way to reduce proteinuria. A systematic review demonstrated that use of aldosterone antagonist given either alone or in concert with other RAAS agents provided significant reduction in proteinuria as well as BP.[82] It should be noted that patients involved in these studies had reasonable kidney function with an eGFR between 57 and 67 ml/min/1.73 m^2. It is unclear whether aldosterone antagonists can be used in patients with more advanced nephropathy, especially given the risk of hyperkalemia.

DIURETICS

Thiazide diuretics have gained a renewed importance in treating hypertension since the publication of the ALLHAT.[88] CKD outcomes were assessed in a posthoc analysis, and no difference in ESRD development between treatment groups was noted, although very few had advanced nephropathy at baseline.[72]

Although JNC 7 makes no specific recommendation about the particular thiazide diuretic used, strong consideration should be given to using chlorthalidone over hydrochlorothiazide. No trial has ever been designed to directly compare the two medications on CKD or CV outcomes; however, almost all the major outcome trials supporting diuretics used chlorthalidone.[88,89] Though the two drugs are thought to have similar efficacy, chlorthalidone is likely more potent because of it longer half-life (44 hours, chlorthalidone vs. 12 hours, hydrochlorothiazide).[90,91] This difference in duration of action translated into an additional 7 mmHg reduction in systolic BP when substituted for hydrochlorothiazide.[90]

A side effect seen with thiazide diuretics is increase in blood glucose levels with a clear risk of diabetes development among obese patients with a baseline fasting glucose of 100 mg/dl or more. There are at least two potential mechanisms to account for this worsening of glucose intolerance, hypokalemia (serum potassium <3.4 mEq/L) and a shift in adipocyte mass.[92,93] However, the increase in glucose at currently used doses is small, and the risk of new onset diabetes is not further decreased when combined with an ACE inhibitor or ARB.[94–96] No study to date has linked thiazide-induced hyperglycemia to higher CV or CKD outcomes.

In general, thiazide diuretics are effective in patients that have estimated GFR of 50 ml/min/1.73 m^2 or more. Loop diuretics should be considered in patients with lower levels of kidney function. Typically, they should be dosed two or three times daily unless using the longer-acting torsemide, but even that may require twice daily dosing for hypertension.

Diuretic resistance is a commonly encountered problem and relates to either underdosing, severe hypoalbuminemia, or heart failure. Classically, the approach to these patients involves increasing the dosage of the diuretic to the appropriate level and combining a loop diuretic with a one that acts at the other parts of the tubule like metolazone. Although this approach is reasonable, an alternative approach is to use a potassium-sparing diuretic, such as amiloride, in combination with a loop diuretic. The rationale behind this is that the chronic exposure to loop diuretics leads to hypertrophy of the epithelial sodium channel in the cortical collecting duct, the target of amiloride.[97]

CALCIUM CHANNEL BLOCKERS

When used in patients without proteinuric kidney disease, both dihydropyridine CCBs (amlodipine or nifedipine) and nondihydropyridine CCBs (verapamil or diltiazem) are effective in lowering BP, and both classes have been shown to lower CV events in high-risk populations.[98] These agents appear to have particular efficacy for CV risk reduction when paired with an ACE inhibitor as evidenced by the results of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.[99] In this trial patients who were at high risk for a CV event and who were treated with a background of maximal ACE inhibition had a 20% relative risk reduction in CV events when treated with amlodipine compared to those treated with hydrochlorothiazide. Similarly, verapamil when paired with an ACE inhibitor is effective in reducing adverse CV outcomes in patients with hypertension and coronary artery disease.[100]

Both preclinical and clinical data demonstrate different effects on kidney physiology between dihydropyridine and nondihydropyridine CCBs in patients who have proteinuria. Dihydropyridine CCBs do not reduce albuminuria and totally eliminate the kidneys ability to autoregulate as compared to nondihydropyridine CCBs, which do lower albuminuria.[101,102] The mechanism of this difference relates to differences in glomerular permeability that occur in patients with advanced nephropathy.[103,104] This difference in antiproteinuric effect has translated into worse CKD outcomes in advanced nephropathy with proteinuria treated with dihydropyridine CCBs when compared to those treated with blockers of the RAAS.[104]

CCBs should not be used to blunt the development of albuminuria or reduce protein excretion in those with microalbuminuria. The BENEDICT trial compared nondihydropyridine CCBs to ACE inhibitors, alone or in combination, in patients with hypertension, type II diabetes mellitus, and normal urinary albumin excretion for development of MAU. No significant effect was seen by verapamil alone on MAU development, the primary endpoint. MAU development occurred with similar frequency in the verapamil and placebo groups.[42] These results were foreseeable as neither class of CCBs have antiinflammatory effects on the

vasculature and as such are unlikely to have any impact on endothelial damage, which is the antecedent of MAU development.[27,105] In contrast, in people with advanced proteinuric nephropathy that cannot tolerate a RAAS blocker, the use of a nondihydropyridine CCB has been shown to reduce proteinuria and slow nephropathy progression.[101,106,107]

In summary, either subclass of CCBs should be used aggressively for BP reduction in patients without proteinuric kidney disease. In those with advanced proteinuric nephropathy, nondihydropyridine CCBs are preferred, per guidelines; however, when dihydropyridine CCBs are used, they should always be in combination with an ACE inhibitor or ARB to maximally reduce proteinuria and BP and slow progression of nephropathy.[11,108]

β-ADRENERGIC BLOCKERS

All advanced nephropathy patients have an increase in sympathetic activity and a high CV event rate. Data clearly indicate a benefit of β-blockers in such patients yet they are not used, a trend that should change to reduce CV risk.[109] Despite being quite effective at lowering BP, clinicians have been reluctant to use β-blockers because of a significant adverse metabolic profile. Some data call into question the use of β-blockers for treating hypertension, although the data are focused on atenolol rather than the class in general.[110] Recent studies demonstrate that excessive reduction in heart rate may be a problem with this class, although more than 80% of the studies quoted were with atenolol.[109]

The emergence of newer vasodilating, metabolically neutral β-blockers may expand the role for their use, especially in diabetes and in those with CKD. The combined α- and β-blocker, carvedilol, and the β-1 vasodilating agent nebivolol have neutral glycemic and lipid parameters. Carvedilol reduces CV morbidity and mortality and the risk of MAU development in those with hypertension and diabetes.[34,111] The mechanism of decreasing MA development likely relates to the antioxidant properties of carvedilol.[112,113] Thus, vasodilating β-blockers can be used in patients with compelling indications, and they are excellent add-on agents to reduce risk and achieve BP targets.

β-Adrenergic antagonists, although effective in reducing BP, have not been shown to slow CKD progression or to consistently reduce albuminuria in either animal models or patients with type II diabetes.[114] This class of agents also fails to reduce CV events in patients with heart failure, as evidenced by the results of the long-acting β-blocker arm of ALLHAT, which was stopped early due to increased events.[115]

CONCLUSION

Preventing progression of CKD should be the focus of both internists and nephrologists. The cornerstone of such therapy is remembering to communicate with the patients so that they understand what they need to do to prevent CKD progression. Specifically, an explanation is needed about salt intake and what the natural history of CKD is so they understand the rationale for why they are taking certain medications. Additionally, in those with established CKD, the major focus should be on: a) adequate 24-hour blood pressure control, b) at least a 30% reduction in proteinuria from when treatment started, and c) the use of agents that inhibit the RAAS. The average number of agents needed to approach the current guideline goal of less than 130/80 mmHg for those with CKD in clinical trials is 3.3 agents at maximally tolerated doses (see Figure 4-5). We must overcome physician inertia and use more fixed-dose combinations if BP is more than 20/10 mmHg above the goal. Data from ACCOMPLISH make a compelling argument for this tenet and also support the use of a combination that does not include a diuretic because the combination of benazepril and amlodipine provided an additional 20% CV risk reduction over the combination of a diuretic and an ACE inhibitor.

There has been concern about the potential risks of aggressive BP lowering, particularly in elderly patients with type II diabetes. Reducing diastolic BP to less than 80 mmHg has been thought to increase CV risk in this group, but no convincing evidence of this possibility was found in prospective clinical trials.[49,116] Retrospective analyses suggested that there might be a J-shaped relationship between diastolic BP and the rate of CV disease mortality in patients with established symptomatic coronary artery disease or unstable angina. However, posthoc analyses of two separate renal outcome trials has failed to demonstrate a J-shaped curve for BP above levels of 115/60 mmHg to 119/62 mmHg.[117] Thus, the putative-shaped curve should not serve as a deterrent to lowering BP to recommended goals in the absence of any clear evidence of coronary disease or unstable angina.

Target BP should be achieved within 3 to 4 months in most patients, but longer periods may be required in those with previous strokes or autonomic dysfunction. BP should be monitored with patients in both the sitting and the upright position to exclude the possibility of orthostatic hypotension, because autonomic denervation is frequent among patients with type II diabetes who have nephropathy and polyneuropathy.

One of the main reasons for the failure to achieve BP goals is inadequate drug dosing or lack of diuretic use. Thus, to optimize CV and CKD risk reduction, physicians should set BP, lipid, and glucose goals with their patients. If possible they should communicate these goals on paper, retain a copy in the chart, and give a copy to the patient. To maximize reduction in CV mortality and progression of renal disease, the patient and the physician should be aware of specific treatment goals and iteratively discuss progress toward them at each visit.

A full list of references are available at www.expertconsult.com.

Chapter 5

CHRONIC KIDNEY DISEASE IN THE ELDERLY

Ann M. O'Hare, M.A., M.D.

This chapter will describe the prevalence and clinical outcomes of nondialysis dependent chronic kidney disease (CKD) in older adults and will discuss key considerations in managing this group of patients.

PREVALENCE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

With advancing age, mean urinary albumin excretion rate increases and mean glomerular filtration rate (GFR) decreases.[1–3] Thus, the prevalence of CKD by definition increases with age, as this condition is currently defined based on fixed estimated GFR (eGFR) and albumin excretion cut points.[4] The age-related increase in the prevalence of CKD is quite dramatic. For example, CKD, which is defined as eGFR less than 60 ml/min/1.73 m^2 or albumin-to-creatinine ratio (ACR) greater than or equal to 30 mg/g, is present in less than 5% of adults under the age of 40 but in more than one third of adults older than age 70 in the general population.[2,3] These differences largely reflect differences between age groups in eGFR, rather than ACR. Age differences in the rate of albumin excretion rea by comparison are quite modest. Consequently, although the majority of younger people who meet criteria for CKD have albuminuria and a preserved eGFR, the majority of older people who meet these criteria have a low eGFR (usually of moderate severity) and do not have albuminuria.[3,5] Thus, a higher proportion of all older patients with CKD by definition have nonproteinuric CKD. This is true both for those with and without diabetes.[3]

Although all stages of CKD are more prevalent in older than in younger individuals, age differences in the prevalence of stage 3 CKD are far more dramatic than they are for other stages. Among elderly individuals with stage 3 CKD, the vast majority have very moderate reductions in eGFR. For example, among patients receiving care in the Department of Veterans Affairs (VA) healthcare system, almost half of all those with an eGFR less than 60 ml/min/1.73 m^2 had very moderate reductions in eGFR in the 50 to 59 ml/min/1.73 m^2 range, and most were older than 75.[6] Among a large cohort of primary care patients in the United Kingdom aged 75 years or older who were enrolled in a large clinical trial, most of those with CKD had an eGFR of 45 ml/min/1.73 m^2 or higher and the vast majority were women. Indeed, kidney disease defined as an eGFR less than 60 ml/min/1.73 m^2 was more common than not in this elderly cohort.[7]

The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines define CKD as an eGFR less than 60 ml/min/1.73 m^2 or kidney damage.[4] Thus, although eGFR criteria for CKD are clearly delineated, "kidney damage" is not clearly defined. In patients with diabetes, microalbuminuria is generally considered to be evidence of kidney damage, but it is uncertain whether this represents a meaningful definition of kidney damage in those without diabetes. Because most elderly people with CKD have a low eGFR, the albuminuria threshold that is equated with kidney damage does not greatly impact estimates of the prevalence of CKD at older ages. However, this threshold does greatly influence estimates of the overall size of the population with CKD and the proportion of the overall population with CKD that is elderly.[3]

For example, those older than 70 years account for more than half of all patients with an eGFR less than 60 ml/min/1.73 m^2, slightly less than half of those with an eGFR less than 60 ml/min/1.73 m^2 or ACR greater than or equal to 200 mg/g and approximately one third of those with an eGFR less than 60 ml/min/1.73 m^2 or ACR greater than or equal to 30 mg/g.[3]

COMORBIDITY IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Chronic kidney disease is classically associated with specific metabolic complications directly related to recognized domains of renal function such as anemia, hyperphosphatemia, vitamin D deficiency, secondary hyperparathyroidism, and acidosis. At the same time, CKD is also known to occur as a result of systemic disease processes and risk factors, such as diabetes, hypertension, infectious diseases such as Hepatitis C virus and HIV, and autoimmune diseases such as systemic lupus erythematosus. However, many of the conditions traditionally associated with CKD, such as vitamin D deficiency, anemia, and hypertension, also occur commonly in older patients who do not meet criteria for CKD.[8–10] At the same time, many age-associated conditions that are less clearly linked to the metabolic functions of the kidney are also quite common in elderly patients with CKD. For example, the prevalence of clinical and subclinical cardiovascular disease, frailty, cognitive insufficiency, functional impairment, and overall burden of comorbidity are all much more common than traditional complications of CKD in the elderly, particularly when eGFR is only moderately reduced.[11–16] In the large elderly United Kingdom cohort described earlier, the number of patients with moderate reductions in eGFR who had cognitive insufficiency, depression, and who had experienced a fall within the recent past were all much higher than the number of patients who had anemia or an elevated phosphorus level.[7] Although some have postulated that CKD may serve as a risk factor for the conditions to which it is epidemiologically linked, it seems more likely that decrements in eGFR serve as a marker for age-related processes such as atherosclerosis, inflammation, and fibrosis capable of impacting multiple different organ systems and functional domains.[17–20] Regardless of the underlying explanation for these associations, it is clear that older patients with CKD have a high prevalence of complex comorbidity. At the same time, the prevalence of complex comorbidity in older patients with CKD (particularly when this is of only moderate severity) may not be substantially higher than among adults of the same age with normal renal function.[7]

CLINICAL OUTCOMES IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Death

Studies in elderly cohorts indicate that eGFR retains considerable prognostic significance for a variety of different clinically significant outcomes in older adults. These outcomes include, but are not limited to traditional renal outcomes such as progression to end-stage renal disease (ESRD) and loss of eGFR. Indeed, other outcomes such as mortality, both cardiovascular and noncardiovascular, cardiovascular events, including stroke, peripheral arterial disease and myocardial infarction, and hospitalization are far more common than progression to ESRD in most older patients with CKD.[21–23] Level of eGFR is also predictive of a variety of other morbid outcomes including hip fracture, frailty, cognitive insufficiency, adverse drug events, and infection.[12,13,24–27] As a result, elderly individuals with CKD not only have more limited life expectancy but are also less likely to age successfully.[22]

However, it is also important to note that the relationship between eGFR and at least some of these outcomes appears to vary systematically with age. At all ages, there is an inverse relationship between eGFR and mortality. However, at any given level of eGFR, absolute mortality rates are higher for older compared to younger patients with CKD.[6,16,28–30] Consequently, mortality rates are extremely high for older patients with severe reductions in eGFR. For example, annual mortality rates in VA patients aged 85 and older with an eGFR less than 15 ml/min/1.73 m^2 were almost 50% per year.[6] On the other hand, relative risk of mortality at any given level of eGFR relative to a referent group with normal renal function is lower in older compared to younger patients.[6] Consequently, at older ages, the threshold level of eGFR below which mortality rises above that of the referent category with an eGFR greater than or equal to 60 ml/min/1.73 m^2 is lower in older than it is in younger patients. For example, in a national cohort of veterans, patients aged 18 to 44 years with an eGFR of 50 to 59 ml/min/1.73 m^2 had a 56% higher adjusted risk of death than their age peers with an eGFR greater than or equal to 60 ml/min/1.73 m^2.[6] On the other hand, mortality risk among members of this cohort aged 65 and older with an eGFR 50 to 59 ml/min/1.73 m^2 was no different than for the referent group. Similarly among a community cohort in Coventry, England, risk of death was no higher for those older than 75 with an eGFR 45 to 59 ml/min/1.73 m^2 than for the referent category with an eGFR greater than or equal to 60 ml/min/1.73 m^2.[30] This phenomenon probably reflects a variety of different factors. Mortality rates in the referent group with normal renal function are higher at older ages. For example, mortality rates in the referent category with an eGFR greater than or equal to 60 ml/min/1.73 m^2 in the VA study described previously, ranged from less than 0.5% for those aged 18 to 44 to almost 10% for those aged 85 and older.[6] Mean level of eGFR among those with an eGFR greater than or equal to 60 ml/min/1.73 m^2 is also lower at older ages. The MDRD equation also has not been extensively validated in adults older than age 70, raising the possibility that age differences in the accuracy of this equation for estimating true GFR may introduce age difference in the prognostic significance of eGFR. Regardless of the underlying explanation, the finding that the threshold level of eGFR below which mortality risk increases above the referent is noteworthy because a large proportion of all older patients with an eGFR less than 60 ml/min/1.73 m^2 have an eGFR above this threshold. For example, in the cohort described by Raymond and colleagues, more than half of all of those with an eGFR less than 60 ml/min/1.73 m^2 had an eGFR 45 to 59 ml/min/1.73 m^2 and had no higher

risk of death than the referent group.[30] Interestingly, the exact relationship between eGFR and mortality at older ages appears to vary with gender. Roderick and colleagues demonstrated that although women with an eGFR 45 to 59 ml/min/1.73 m^2 experienced no greater risk of death than women in the referent category, risk of death for men with an eGFR 45 to 59 ml/min/1.73 m^2 was slightly higher than for the referent category.[7]

Progression

The relationship between eGFR and progression of CKD also appears to vary with age. Age is a leading risk factor for progression to ESRD, and most patients who reach ESRD are older than 60 years.[31] However, this pattern largely reflects the higher prevalence of CKD at older ages. When older and younger patients with similar levels of eGFR are compared, patients older than 65 years with an eGFR less than 60 ml/min/1.73 m^2 are less likely to progress to ESRD than their younger counterparts.[28,32,33]

However, the relationship between age and progression to ESRD appears to be somewhat dependent on level of eGFR yielding seemingly conflicting observations in the literature. Among patients with higher levels of eGFR, the risk of ESRD appears to be higher in middle-aged adults than in younger adults.[28] Thus several authors have reported a positive association of age with progression based on findings in cohorts with relatively preserved levels of eGFR. For example, in a community screening cohort with a mean age of 41 years and a mean serum creatinine of 1 mg/dl, Hsu and colleagues demonstrated that risk of progression to ESRD was higher in middle-aged than in younger adults.[34] Nevertheless, even in this cohort, rates of progression among those older than 65 were lower than for either of these age groups. Similarly, Ishani and colleagues reported a higher risk of ESRD among younger compared with older screenees in the Multiple Risk Factor Intervention Trial with each 10-year increase in age conferring a roughly twofold increased risk of ESRD.[35] However, members of this cohort were all between the ages of 35 and 57 and had a mean age of 46 years. Mean eGFR in this cohort was approximately 79 ml/min/1.73 m^2.

Onset of ESRD is a complex outcome as it represents both a measure of disease severity and a treatment decision, and it is possible that treatment decisions may vary by age. However, the relationship between age and rate of change in eGFR appears to be reasonably consistent with that between age and progression to ESRD, particularly among patients with more severe CKD. Among patients with an eGFR less than 45 ml/min/1.73 m^2, older age also appears to be associated with a slower rate of decline in eGFR.[28] However, measurement of this outcome is quite sensitive to the method used to calculate rate of change in eGFR and the baseline level of eGFR among study participants. Among patients with preserved eGFR, loss of eGFR appears to be faster among older patients, while the reverse is true among patients with lower levels of eGFR.[28,32]

At any given level of eGFR, older patients are more likely to die and less likely to progress to ESRD than their younger counterparts.[28,32] Their lower risk of progression appears to reflect both a higher competing risk of death and slower rates of progression, particularly among those with lower levels of eGFR. In addition, age may also influence the likelihood that a patient with indications for dialysis receives this therapy. It is possible that lower rates of ESRD among older patients may also reflect age differences in the decision as to whether to initiate dialysis. Regardless of the underlying explanation, the relationship between eGFR and death and ESRD varies by age. In younger patients, ESRD is a more common outcome than death even among patients with moderate reductions in eGFR (30 to 44 ml/min/1.73 m^2). On the other hand, among patients older than 85, death is a more common outcome than progression to ESRD even among those with advanced kidney disease.[28]

PROGNOSTIC IMPORTANCE OF CHANGING ESTIMATED GLOMERULAR FILTRATION RATE

Most studies have measured the association of eGFR with clinical outcomes based on ascertainment of eGFR at a single point in time or averaged over time. However, several recent studies suggest that dynamic changes in eGFR also have prognostic significance.[36,37] Among participants in the Cardiovascular Health Study, a community cohort of elderly Medicare beneficiaries, those who experienced the most rapid change in serum creatinine measurements experienced the highest death rates.[37] Among a Norwegian community cohort, prognosis was impacted by the time frame used to define chronicity low eGFR measurements. Requiring longer time periods between serum creatinine measurements (e.g., 6, 9, or 12 months vs. 3 months) to define a target population tended to capture subgroups with progressively higher rates of progression to ESRD and lower death rates.[36]

PREDICTING THE COURSE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

In the elderly, CKD rarely occurs in the absence of other age-related comorbid conditions such as hypertension, vascular disease, and diabetes. For a variety of reasons, it is often difficult to ascribe a single underlying etiology to CKD in an older adult. Older patients often have more than one condition that can be associated with CKD, and their level of kidney function can often reflect the effect of cumulative insults to the kidneys over the course of a lifetime (e.g., analgesic nephropathy, nephrectomy, and hypertension). In many elderly adults CKD may more often function as a marker for coexisting age-related processes than for a dominant primary renal disease process. Thus, the paradigm of a single disease process having a dominant effect on clinical outcomes may be less helpful in older than in younger adults. This principle has implications for how we predict the course of and manage CKD in the elderly. For example, it may be very difficult to predict the course of CKD in an older person if the CKD is largely determined by nonrenal factors. Ishani and colleagues recently demonstrated that hospitalized acute kidney injury among elderly Medicare recipients is a leading risk factor for progression to ESRD, particularly among patients with existing CKD.[38] A recent metaanalysis demonstrated that

older patients who experience an episode of acute kidney injury are less likely than younger patients to regain their preadmission level of renal function.[39] Collectively, these studies suggest the possibility that at least in a subset of elderly patients, progression to ESRD does not occur in a linear predictable fashion but rather as a result of repeated and unpredictable episodes of acute kidney injury.

RELEVANCE TO OLDER ADULTS OF CURRENT GUIDELINES FOR THE MANAGEMENT OF CHRONIC KIDNEY DISEASE

Current guidelines for the management of CKD do not take into account age differences in the frequency of different clinical outcomes or in the prevalence of complex comorbidity in the elderly.[4] Related to this, there are several important considerations in evaluating the relevance of these guidelines to older adults with a low eGFR.

First, the current CKD paradigm is based on the assumption that patients at similar stages of CKD face a roughly equivalent risk of experiencing clinically significant outcomes and will thus benefit from similar interventions. However, as discussed earlier, age is a major effect modifier among patients with CKD, and older patients have a very different absolute risk for different clinical outcomes than their younger counterparts. In addition, the frequency of a given outcome both relative to other outcomes and relative to the frequency of that outcome in patients of the same age with normal renal function varies markedly with age.

Second, CKD in the elderly rarely occurs in the absence of other comorbidities. Indeed, coexisting comorbidities are often far more common than the traditional complications of CKD and are not necessarily causally linked to underlying kidney disease. The high prevalence of complex comorbidity in elderly patients with CKD may impact the relevance of a disease-based approach by increasing the number and complexity of competing health concerns. At the same time, heterogeneity in the level of comorbidity within the elderly population with CKD may preclude the development of uniform treatment strategies that are applicable to all older adults with CKD.

Third, little published evidence is available to support recommended treatment strategies in older patients who meet criteria for CKD. Management of CKD is challenging in part because there have been so few randomized controlled trials to support specific management strategies.[40] However, even in areas where evidence from randomized controlled trials does exist, these studies have tended to exclude older patients. For example, most trials that have been used to support the use of ACE inhibitors and ARBs in patients with CKD were conducted in young and middle-aged adults.[3] Furthermore, many of these trials favored enrollment of participants with proteinuria.[3,41] However, with increasing age, a decreasing proportion of all patients who meet criteria for CKD have proteinuria. Because proteinuria is a critical determinant of both progression and of the effect of ACE inhibitors and ARBs on progression, it is not clear how generalizable the results of these trials and associated guidelines are to the elderly.

APPROACH TO THE MANAGEMENT OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

Age differences in the associated features and in outcomes associated with CKD seem to suggest that a single approach based primarily on eGFR will not be equally appropriate for patients of all ages. Older patients with severe reductions in eGFR are less likely than their younger counterparts to progress to ESRD and are often at far greater risk for morbidity and mortality. Thus guidelines for the management of CKD that are based primarily on preparation for ESRD are less likely to be applicable to older patients. Conversely, older patients with very moderate reductions in eGFR are no more likely to die than are their counterparts with higher levels of eGFR. They are also at lower risk for progression than their younger counterparts. Thus management strategies aimed at reducing cardiovascular risk and slowing progression of CKD may be less appropriate for older than for younger members of this group. At the same time, heterogeneity within the elderly population with CKD suggests that no single management approach will be equally appropriate for all older patients who meet criteria for CKD.

Tinetti and Fried have argued that disease oriented models of care are not appropriate for the management of complex comorbidities in the elderly.[42] As illustrated by Boyd and colleagues, the application of disease specific management strategies to a hypothetical older patient with complex comorbidity can result in an onerous treatment regimen with a high potential for adverse drug effects.[43] Tinetti and Fried argue for an individualized integrated care model that takes into account the coexistence of multiple different comorbidities, multiple different and often competing outcomes, heterogeneity among older patients, and differences in patient preferences.[42] In this model, whether or not a person has a particular disease becomes less relevant than whether they are at risk for significant outcomes. The authors point out that an individualized care model does not preclude the implementation of disease-specific management strategies, particularly if these will have an impact on outcomes that are important to the patient.

Thus, although many recent studies have emphasized wide-ranging associations between CKD and other health conditions, these findings collectively tend to lessen the relevance of a disease-oriented approach for older patients who meet criteria for CKD and instead argue for an individualized approach in this population.[44] Although a kidney disease-specific approach is unlikely to be appropriate for all older patients who meet criteria for CKD, it is clear that such strategies are needed for some older patients who meet criteria for CKD. Most patients who reach ESRD are elderly, and the size of the elderly population with ESRD is increasing. Older patients who reach ESRD tend to experience worse health outcomes compared to their younger counterparts and are less likely to be able to receive a kidney transplant.[45,46] Indeed, there is some question about whether dialysis truly prolongs survival in very elderly patients with a high burden of comorbidity. Furthermore, a substantial number of older patients who reach ESRD do not receive appropriate pre-ESRD care, suggesting that there may be considerable room for outcome improvement in this group.[47]

Thus, a major challenge facing clinicians caring for older patients lies in identifying the relatively small proportion but large number of older adults with CKD who are at greatest risk for progressing to ESRD. Broad-based proactive efforts to identify patients with earlier stages of CKD at risk for progression to ESRD are not likely to be as effective in older as in younger patients because the vast majority will not progress to ESRD and thus will not benefit from efforts to reduce cardiovascular risk. Even efforts targeted at those with severe reductions in eGFR may not represent the best approach because most of these patients also will not progress to ESRD. Nevertheless, identifying the small subset of elderly patients with progressive disease who are most likely to benefit from efforts to prevent progression and prepare for the development of advanced renal failure must be a goal of any individualized treatment strategy.

CONCLUSION

CKD, based on eGFR and albuminuria criteria, is prevalent in the elderly. The prevalence of complex comorbidity in older patients who meet criteria for CKD is high, and most are much more likely to die than to progress to ESRD. For many of these patients, renal-disease specific treatment strategies focusing on the metabolic complications or progression of CKD may not represent the most meaningful or important part of their care, particularly if they have multiple different competing health concerns and priorities. At the same time, a subset of elderly patients with CKD will experience progressive CKD, and they account for a large and growing portion of the ESRD population. Although many of these patients will also have complex comorbidity and would benefit from an individualized treatment strategy, a disease-specific approach may have greater potential value and may assume a more prominent part of their care plan. Thus, caring for older patients with CKD presents several challenges including the identification of the subset of patients most likely to benefit from disease-specific treatment strategies, evaluating the quality and generalizability of evidence to support recommended disease-specific interventions, and, in many instances, evaluating the value of such disease-specific treatment strategies in the context of complex comorbidity, potentially competing health concerns, and limited life expectancy.

A full list of references are available at www.expertconsult.com.

Chapter 6

THE ROLE OF THE CHRONIC KIDNEY DISEASE CLINIC

Monica C. Beaulieu, M.D., F.R.C.P.C., M.H.A., Bryan M. Curtis, M.D., F.R.C.P.C. and Adeera Levin, M.D., F.R.C.P.C.

The purpose of this chapter is to outline the structure and function of a clinic-based approach for the comprehensive care of patients with chronic kidney disease (CKD) and describe some of the potential uses of such a clinic. The described structure and function may serve as a template for the development of such clinics. To ensure a context for such a clinic, we also review the evidence and rationale supporting this concept. Unlike the paradigm for diabetes or heart failure, the role of a clinic facilitating the care of patients with CKD has not been as clearly defined. Thus, data to support the concept and implementation are relatively scant, with much being drawn from logical arguments and from experience with other chronic diseases.

This chapter will describe CKD as an important health problem, key goals of care, and the evidence on which these goals are founded. It also will describe the principles of chronic disease management and a model of integrated multidisciplinary team-based care structured on these goals. To complete the chapter, we will review ongoing and future clinical trials to ensure that the reader is prepared for upcoming publications.

KIDNEY DISEASE IS AN IMPORTANT HEALTHCARE CONCERN

The burden of disease and the growing population of patients with end-stage renal disease (ESRD) remain exceedingly high. In the United States a diagnosis of ESRD may impart more lost life years than prostate or colorectal cancer.[1] As of 2008 in the United States, there were over 328,000 patients on dialysis, and over 18,000 kidney transplants performed per year.[2] Current estimates reveal that approximately 8% to 10% of the general population has some degree of impaired kidney function.[3–6] Population studies such as the National Health and Nutrition Examination Survey (NHANES) III cross-sectional survey of 29,000 persons revealed that 3% of people over age 17 had elevated creatinine.[7] It is estimated that by 2030, the number of patients with ESRD may reach 2.24 million.[2] Furthermore, the direct cost of caring for a patient on dialysis can cost over $65,000 (U.S.) annually.[2,8,9]

KIDNEY DISEASE IS LARGELY DUE TO CHRONIC DISEASES

In North America CKD is largely due to diabetes and hypertension,[2] both of which are relatively easy to identify and treat with evidence-based interventions. Furthermore, clinical trials and prospective cohort studies have identified risk factors associated with accelerated loss of kidney function. In patients with CKD secondary to diabetic, glomerular, and hypertensive or vascular diseases, the strongest predictors of more rapid progression are hypertension, especially systolic,[10–18] and the degree and persistence of proteinuria.[19–22]

Historically, the focus of CKD care was to coordinate placement of vascular access, to attend to uremic symptoms and complications, and to provide dialysis. However, the focus has changed; not only is it increasingly recognized that the majority of patients with CKD do not progress to ESRD due to varying rates of progression[15,21] and competing risks for death,[23] but also conditions associated with CKD itself, such as anemia and malnutrition, impart significant morbidity. Moreover, there is now a greater appreciation of the epidemiology of the disease, which has led clinicians to understand that the major competing risk for dialysis therapy is death from cardiovascular disease (CVD). Evidence has accumulated regarding the need for more proactive care and for the institution of strategies to delay progression. Thus, the focus of CKD care has broadened to include CVD risk reduction, in addition to or concomitant with, reducing the progression of kidney decline.[24] As our understanding has grown of the pathophysiology of kidney disease and CVD within the CKD population, it has become clearer that the treatment and care options are increasingly complex. In addition, it was logical that identification and intervention of individuals in the population with earlier stages of CKD would provide the greatest opportunity to reduce morbidity and mortality.

GOALS OF THERAPY

The goals of therapy (Figure 6-1) are to 1) delay progression of CKD, 2) delay and treat known CVD comorbidities, 3) manage uremic complications (such as anemia, mineral metabolism abnormalities, malnutrition, and elevated blood pressure), 4) ensure modality choice and timely placement of access or transplant workup, and 5) initiate timely kidney replacement therapy, including preemptive transplantation where feasible. Each of these goals requires education of patients and caregivers, communication between them, and comanagement by different caregivers within medicine, including allied health professionals. With the main aim to maintain health, it is essential that the structure of the clinic reflect all goals and the demand for communication and investigation to ensure success.

STAGING AND TERMINOLOGY FOR CHRONIC KIDNEY DISEASE AND IMPACT ON NEED FOR COORDINATED CARE

In 2002 the National Kidney Foundation sponsored Kidney Disease Outcomes Quality Initiative (K/DOQI) published guidelines targeting earlier evaluation and intervention in patients with CKD.[25] Using evidence-based review, the cornerstone of the working group was the establishment of five stages of kidney disease (Table 6-1). Importantly, the classification system focused on estimated glomerular filtration rate (eGFR) rather then serum creatinine levels alone, because use of serum creatinine alone may lead to overestimation or underestimation of kidney function in those with low (i.e., elderly, women) or high (i.e., muscular males, blacks) muscle mass, respectively. The new system bases the classification not only on severity of kidney function decline, but also on the presence of conditions associated with the kidney disease, such as proteinuria. The adoption of this staging system has helped clarify the previously used terms (predialysis, progressive renal disease, progressive renal

TABLE 6-1 Five Stages of Chronic Kidney Disease

STAGE	GFR (ml/min/1.73 m²)	DESCRIPTION
1	>90	Kidney damage with normal or ↑ GFR
2	60–89	Kidney damage with mild ↓ GFR
3	30–59	Moderate ↓ GFR
4	15–29	Severe ↓ GFR
5	<15 (or dialysis)	Kidney failure

↑, increased; ↓, decreased.
Adapted from K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative, Am. J. Kidney Dis. 37 (2 Suppl. 2) (2002) S1-246.

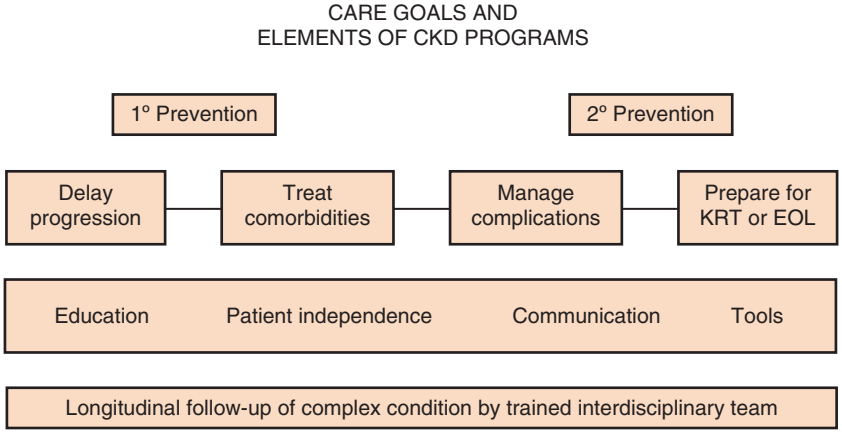


FIGURE 6-1 Care goals and elements of CKD programs. EOL, End of life. KRT, Kidney replacement therapy.

insufficiency), which were often confusing and sometimes misleading. The use of a universal language and terminology has helped facilitate knowledge acquisition by the medical community, patients, and public bodies and has improved research clarity and applicability.

The estimates of populations with CKD generated from the new classification system and the accompanying public awareness campaign around the world have helped identify the large burden of CKD that exists. The focus on earlier identification has identified a large number of patients, and with this the need to create appropriately structured care delivery systems described herein, including the education of other health care providers in CKD care.

REFERRAL

Late referral to nephrology has been recognized as a problem for many years, because it is associated with increased cost and suboptimal patient outcomes.[26–29] Published recommendations emphasize timely referral to maximize potential gains from involvement of specialized nephrology teams.[30] The appropriate time of referral to a nephrologist is debatable for many reasons, including: 1) other physicians should be capable of managing earlier stages of CKD, 2) estimated high numbers of patients overwhelm current nephrology resources, and 3) many patients with early stages of CKD may not progress. Nonetheless, a minimum recommendation would be for referral at eGFR levels of less than 60 ml/min/1.73 m^2 if the primary caregiver cannot identify the cause of the disease or requires help in the management of disease. All patients with an eGFR less than 30 ml/min/1.73 m^2 should be seen by a nephrology team to ensure adequate psychological and clinical preparation for kidney replacement therapy[30,31] unless the patient is of an age or has a condition that leads them to not consider chronic dialysis. The new CKD staging system focused on GFR estimation should reduce some of the problems of late referral due to misinterpretation of serum creatinine values.

OVERVIEW OF CHRONIC KIDNEY DISEASE CLINIC

Philosophical Basis

Clinics for the care of CKD should be based on the fundamental principle of ensuring the delivery of longitudinal, complex care to a large, diverse group of individuals. This requires that the structure of the clinic and services offered optimize communication within and between individuals, including the patient and other physicians and medical teams. One of the key roles of the care should be to integrate medical, psychological, and social aspects of chronic disease to optimize patient outcomes.

Role of Multidisciplinary Clinics

The importance of early referral to nephrologists is not disputed,[28] because identification of the myriad of abnormalities and plans for their treatment is best achieved in consultation with a specialist. However, the ability of nephrologists "alone" to attend to the multiple and complex aspects of care in this patient group is debated.[32] A multicenter cohort of patients starting dialysis demonstrated that even those patients known to nephrologists for greater than 3 months have suboptimal care. In this study, one third did not have permanent access ready for dialysis initiation, mean hemoglobin was 94 g/L, and mean albumin was below 34 g/L.[33] In another multicenter study of patients with CKD followed by nephrologists, the majority of patients had blood pressure over recommended targets, and only 50% were taking angiotensin-converting enzyme (ACE) inhibitors. Furthermore, despite a history of significant heart disease and 66% prevalence of dyslipidemia, only 22% of at-risk patients were on lipid lowering medications. Abnormalities of calcium, phosphate, and parathyroid hormone levels were also demonstrated with only 15% of patients receiving therapy.[34] Although there are undoubtedly patient and adherence factors that explain why patients with CKD under the care of nephrologists do not have optimal care, it is also probable that patients were not provided the appropriate elements of care. It is important to note, however, that it was these studies and others that contributed to the recognition of the importance of CKD care and the lack of attention to it.

Given the multiplicity of goals of CKD care, the complexity of treatment options, and educational needs, it is clear that a team of individuals will be required. Treatment targets, such as blood pressure, may be reached by involving expert nurses, pharmacists, or other members of the team in conjunction with the physician.[35] Thus, a team approach with well-defined roles, responsibilities, and objectives appears to be both logical and practical. Improved patient care and outcomes due to a multidisciplinary team clinic have been demonstrated in disciplines such as diabetology,[36,37] cardiology,[38–40] rheumatology,[41–43] and oncology.[44] Similarly, compared to standard care by a nephrologist alone, there is evidence of benefit of a multidisciplinary care (MDC) team approach in the care of patients with CKD.[45–50] It appears that outcomes can be improved with protocol-based blood work, clinic visits, and education. This requires involvement of a patient educator, dietitian, social worker, pharmacist and physician.

Structure and Definition of Multidisciplinary Clinics

These definitions help to clarify the definition of a multidisciplinary team as intended by the authors. It allows the readers to determine what type of resources they currently have available and may help in the interpretation of clinical studies so that similar types of clinics can be compared. Clinic structures can be categorized as follows with respect to multidisciplinary teams:

Formal Multidisciplinary Team

A multidisciplinary team is defined as nurses, nurse educators, dietitians, pharmacists, social workers, and physicians who are allied in a formal relationship and who interact with the patient and each other. Although it is recognized that there are a number of different configurations due to funding and local health care system issues, for the purpose of

definition, this team is readily identifiable as dedicated (part time or full time) to CKD care, and it may or may not have team rounds or meetings to discuss patient care.

Informal Multidisciplinary Resources

Nurses, social workers, dietitians, pharmacists and physicians associated with the kidney team to whom patients are referred may constitute informal resources. In such a schema, patient access is dependent on individual patient needs, and the group of individuals may or may not interact as a team or be necessarily dedicated to the longitudinal follow-up of patients. Each team member is able to interact with the patient on a regular basis as necessary, but no coordination with other team members is inherent to its structure.

No Multidisciplinary Team

Nurses, social workers, pharmacists, and dietitians may or may not be available to the patient. There is no team structure or function.

KEY GOALS OF CHRONIC KIDNEY DISEASE CARE

The following section describes the key goals of comprehensive CKD care, citing the evidentiary basis as appropriate for the described strategies, including diagnosis, education, delay of progression, identification and treatment of comorbidities associated with CKD, and of complications of CKD. The institution of primary prevention strategies, including vaccination programs and the preparation of patients for renal replacement therapy as appropriate, will also be discussed. The goals described are comprehensive and complex, thus the need for a structured delivery system with protocols, such as a formal clinic.

Diagnosis

The first goal of the nephrology clinic medical staff should be to attempt to establish or confirm a diagnosis and to determine the rate of progression of kidney disease.

The nephrologist should ensure that appropriate tests have been undertaken to establish a diagnosis. Kidney biopsy or imaging may be helpful,[30] especially to rule out any potentially treatable or reversible etiologies such as rapidly progressive glomerulonephritis or obstruction. In early visits, reversible causes of kidney disease should be sought, even if a chronic etiology is suspected, especially if there has been a rapid decline in kidney function. In addition to diagnostic tests, review of current medications to ensure the absence of nephrotoxic medications is prudent. Further workup includes a review of family history and medications and a search for systemic disease, including diabetes, vascular disease, connective tissue disorders, infections, and malignancy. Several contributory factors may coexist. The extent of comorbidities, especially the commonly associated vascular diseases,[51] should be continually assessed. Although established kidney disease may progress even if the original cause is removed,[52] similar interventions that can slow the loss of kidney function may prevent cardiovascular complications.

Education

Patient education and awareness are integral components of the clinic. Education is important from a decision-making perspective and to alleviate fear and psychological suffering. Educated patients are more likely to take an active part in their care, with better outcomes noted in other chronic diseases.[53–55] Ideally, involvement of family members or other support network individuals should be encouraged. The clinic environment can provide a set of resources and sessions related to patient education. Minimal education should include the following, which should be presented at the appropriate stages of CKD:

- Explanation of normal kidney function, blood pressure, and laboratory test results and their significance
- Explanation of specific disease conditions, symptoms, and complications of CKD
- Dietary teaching and diabetes education, if appropriate
- Ensuring that patient understanding of medications is adequate
- Discussions about vein preservation (blood taking and blood pressure)
- Erythropoietin hormone therapy teaching, including importance of anemia and its treatment, dose changes; side effects of iron therapy, self-administration or local administration by the primary care provider or community nurse, and provision of educational materials to the primary care provider
- Discussion of choices for treating ESRD, including conservative therapy, hemodialysis, peritoneal dialysis, and transplant and discussion of the benefits of home based modalities, if appropriate
- The education effort can be augmented with pamphlets or video materials. Using the principles of adult learning, regular reinforcement of the key messages should be incorporated into the education program.

Delay of Progression

The cornerstone of CKD care is to delay progression of kidney disease and, thereby, to reduce complications related to kidney failure. The evidence is relatively consistent in citing that interruption of the renin-angiotensin system is a key component to delaying progression. Control of hypertension and reduction of proteinuria are important consequences of renin-angiotensin system interruption and are described more fully later. Potentially nephrotoxic interventions, such as iodinated intravenous contrast dye, must be reviewed with the patient so that educated decisions may be made regarding their use.

Hypertension Treatment

Blood pressure goals should be based on the average of two or more seated readings on each of two or more office visits.[56] There is substantial evidence to support the optimal and target blood pressure of less than 130/80 mmHg in patients with established kidney disease, as suggested in the guidelines of the Seventh Joint National Committee for Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[15,56–61] The goals are to reduce the rate of

decline of kidney function[62] and to decrease cardiovascular events and mortality. Patients with proteinuria greater than 1 g/d may benefit from even lower blood pressure targets (i.e., less than 125/75).[59] This is based on evidence of slower progression of kidney failure at this level of blood pressure in a large randomized trial, which showed the greatest gain in those with the most proteinuria.[15,16] Patients with kidney disease often need three to four different medications in addition to lifestyle modification in order to achieve this goal.[61] ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics are key drug classes for achieving blood pressure control.[15,62–65]

Proteinuria Reduction

Patients with CKD and persistent proteinuria of greater than 3 g/d may progress to requiring dialysis or transplant within 2 years.[10,66,67] A number of large, randomized, controlled trials demonstrated the efficacy of ACE inhibitors in slowing progression of kidney disease, reducing proteinuria, and also in regressing left ventricular hypertrophy.[68–74] Because some of these trials were placebo-controlled, it is difficult to be sure that the benefit was drug specific and not just due to blood pressure lowering. Nevertheless, follow-up studies suggest that long-term ACE inhibition, as a component of a blood pressure therapy, can be associated with stabilization and even improvement of kidney function.[74] Prophylactic use can also be justified in type 2 diabetes, because ACE inhibition preserved kidney function for over 6 years in normotensive patients with type 2 diabetes without microalbuminuria.[75] More recently, the use of angiotensin receptor blockers (ARB) have been shown to reduce the time to doubling of serum creatinine, reduction of proteinuria, and time to dialysis.[63,64,76] All of these studies have been performed in patients with diabetes. Mann and associates[77] have demonstrated the usefulness of ACE inhibitor use in patients with established CVD, diabetes plus one risk factor, and kidney disease, in a subanalysis of the HOPE study. One trial demonstrated that dual blockade of the renin-angiotensin system with both an ACE inhibitor and an angiotensin-II receptor blocker (vs. monotherapy and placebo) may offer additional renal and cardiovascular protection in patients with type I diabetes and diabetic kidney disease.[76] However, dual therapy with both an ACE inhibitor and an angiotensin-II receptor blocker must only be done with careful monitoring of renal function and serum potassium, because one study[78] has suggested an increased risk of renal failure and hyperkalemia when used in high-risk patients with hypertension.

Management of Comorbidity: Secondary Prevention

These topics are covered in-depth by individual chapters as noted.

Cardiovascular Disease (See Chapter 10)

Patients with CKD have significant morbidity and mortality from CVD and are more likely to die than require renal replacement therapy.[79] For example, cardiovascular death is 25 times more common than death due to kidney failure in Type 2 diabetics with microalbuminuria[80] CKD is an independent risk factor for the development of coronary artery disease,[81–83] and it is also associated with an adverse effect on prognosis from CVD.[84,85] In addition, it is well known that "traditional" cardiac risk factors such as diabetes, smoking, hypertension, and dyslipidemia are highly prevalent in the CKD population.[78] In addition, CKD complications such as increased arterial stiffness, uremic toxins, anemia, bone and mineral metabolism abnormalities, and proteinuria have been identified as potential contributors for the increased risk of CVD in CKD patients.[84,85] Reversible cardiac risk factors, identified in these earlier stages, persist following entry to dialysis. Left ventricular hypertrophy occurs in the CKD population, and its prevalence is inversely related to the level of declining kidney function.[86,87] Anemia and hypertension are also risk factors for progressive left ventricular growth.[87] In kidney transplant recipients, a model of CKD, hypertension is a risk factor for left ventricular growth, de novo heart failure, and de novo ischemic heart disease.[88–91]

The National Kidney Foundation convened a task force in 1997 to specifically examine the epidemic of CVD in CKD.[92] With a focus on decreasing death rates via strategies for prevention of disease, the task force considered whether strategies learned from the general population are applicable to patients with CKD. Recognized traditional risk factors identified in the general population include diabetes, hypertension, smoking, family history of coronary disease, male gender, older age, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, physical inactivity, menopause, and psychological stress (Table 6-2).

As CKD progresses, additional risk factors related to chronic uremia also emerge. Excess CVD risk may also be due to hemodynamic and metabolic perturbations, including fluid overload, anemia, malnutrition, hypoalbuminemia, inflammation, dyslipidemia, prothrombotic factors, hyperhomocysteinemia, increased oxidative stress, divalent ion abnormalities, vascular calcification, and hyperparathyroidism.[93,94]

Patients with CKD therefore require assessment and therapy for vascular disease and associated risk factors. It should be noted that many risk factors for CVD are also associated with the risk of progression of CKD.[95] Thus, risk factor reduction strategies used to prevent CVD in the general

TABLE 6-2 Risk Factors for Cardiovascular Disease*

TRADITIONAL	UREMIC
Diabetes	Hemodynamic overload
Hypertension	Anemia
History of smoking	Malnutrition
Family history of coronary disease	Hypoalbuminemia
Male gender	Inflammation
Older age	Prothrombotic factors
Dyslipidemia	Hyperhomocysteinemia
Proteinuria	Increased oxidative stress
Physical inactivity	Divalent ion abnormalities
Menopause	Vascular calcification
Psychological stress	Hyperparathyroidism
Progression of CKD	

*As CKD progresses there is a parallel evolution of risk factors from traditional to those characteristic of chronic uremia.

population can be applied to patients with CKD and may slow the progression of kidney disease, as well.[95–96] It remains unclear whether a raised serum creatinine is a marker for more severe hypertension, diabetes mellitus, and vascular disease, which causes death, or a marker for some intrinsic property of kidney disease, which accelerates CVD. However, some factors more peculiar to kidney disease (anemia, hypoalbuminemia, dyslipidemia) induce cardiac risk and may be amenable to intervention.

Anemia (See Chapter 7)

It has become increasingly evident that anemia is an important predictor of morbidity and mortality in the dialysis population.[96–98] It is associated with ischemic heart disease, left ventricular hypertrophy, and impaired quality of life.[96,98,99] Correction of anemia in CKD improves physical function, energy, cognitive function, and sexual function.[96,100] Treatment of CKD patients with anemia involves using iron supplementation in early kidney disease to maintain erythropoiesis. Erythropoietin stimulating agents (ESAs) effectively increase hemoglobin in patients who are iron replete but remain anemic.[96,98–106]

ESAs are currently recommended in patients with CKD who are iron replete for partial correction of anemia. There have been several studies investigating the optimal target hemoglobin for patients with CKD who are treated with ESAs. Two studies looked at whether normal or near normal hemoglobin should be targeted in CKD.[107–108] Theses studies actually showed an increased risk of adverse outcomes with normal or near normal hemoglobin levels. On further analysis, the adverse outcomes with higher hemoglobin levels may be related to the high doses of ESAs necessary to achieve these targets in some patients.[109] Most current CKD guidelines use a hemoglobin target of 110 to 120g/L, with caution not to exceed greater than 130 g/L.[110]

Mineral Metabolism (See Chapter 8)

There is evidence to support the efficacy of calcium and vitamin D supplementation for treatment of hyperparathyroidism.[111–114] Currently, recommendations regarding target values for patients with earlier stages of CKD have been extrapolated from those for patients with ESRD. We propose an approach that attempts to prevent hyperparathyroidism and its associated long-term complications. Phosphate reduction using dietary restriction, and inexpensive phosphate binders/calcium supplementation in those who have evidence of elevated intact parathyroid hormone and low normal calcium levels are reasonable. Vitamin D analogues are useful for those in whom parathyroid hormone remains elevated despite calcium supplementation and phosphate restriction. Physiological release of hormones is pulsatile and, thus, intermittent oral vitamin D therapy is recommended. Unfortunately, evidence for the effectiveness of therapeutic strategies and for specific target levels of each of the variables mentioned previously is not available for earlier stages of CKD. Adherence to the principle of prevention, combined with early identification of calcium, phosphate, and parathyroid hormone abnormalities at early stages of CKD, should lead to minimizing hyperplasia of the parathyroid glands and the attendant metabolic derangements. Future studies will need to address long-term targets and therapeutic strategies.

Nutrition (See Chapter 12)

Malnutrition is common in patients with later stages of CKD. There is a strong association between decreased albumin and worse nutritional status, and adverse outcomes.[100,115–118] Even small decreases in albumin are associated with increased mortality. Unfortunately, albumin is a late index of malnutrition and is a negative acute phase reactant. Acidosis is also a contributor to protein breakdown and mineral metabolism aberrations. Thus, assessment of nutritional status generally requires the expertise of a dietitian.

Reduced protein diets have been extensively studied as a means to slow the progression of kidney disease, with mixed results. Meta analyses and a large, randomized trial suggest that the impact may be slight.[119–120] Optimal dietary protein intake is not clear,[119] and there is a potential for protein malnutrition. Appropriate nutritional counseling to avoid malnutrition, acidosis, and phosphate excess is important. There are extensive guidelines for assessment of nutritional status and dietary management proposed by the National Kidney Foundation.[121] Ensuring adherence to a prescribed diet is difficult and requires frequent, continuous input from dietitians. This becomes especially important as the patient approaches ESRD, because worsening malnutrition may become the principal indication to initiate dialysis.

Management of Comorbidity: Primary Prevention

These topics are covered in-depth by individual chapter as noted.

Primary prevention strategies are also important in the management of patients with CKD and may sometimes be overlooked due to the time-intensive management of conditions associated with uremia. Vaccinations, use of aspirin and lipid lowering agents and other CVD primary prevention strategies, diabetes control, smoking cessation, and lifestyle modification are important. This section briefly touches on these strategies in CKD patients.

Vaccinations

Hepatitis B infection remains a concern in dialysis populations, and current recommendations are to vaccinate eligible patients. In addition, there are recommendations to vaccinate patients with CKD against pneumococcal infections and influenza, which are common sources of morbidity in patients with chronic illnesses. Vaccination programs have been less successful among CKD patients compared to the general population, both in terms of implementation and response to vaccine. Reasons for poor response include malnutrition, uremia, and the generalized immunosuppressive state of patients with CKD. However, variations in vaccination dose and dosing schedule to increase response rates in dialysis patients have been tried with reasonable success, which could be implemented among patients at all stages of CKD. In general, patients with higher eGFR levels are more likely to respond with seroconversion to hepatitis B[122] and other vaccines. This reinforces the need to identify CKD early and to provide comprehensive care.

Aspirin

The use of low-dose aspirin should be considered to reduce the risk of subsequent CVD in patients with coronary artery disease or in those who are at high risk of developing coronary disease,[92] which includes most patients with CKD. Recommendations to use aspirin should take into consideration the individual patient's risks of bleeding or other complications of aspirin. If there are contraindications to aspirin use, then the use of other antiplatelet agents could be considered.

Dyslipidemia

There are no trials showing that treating dyslipidemia slows the progression of kidney disease. Based on randomized trial evidence of CVD protection, current guidelines recommend an aggressive approach to lipid abnormalities in diabetic and other high-risk patients, which would include those with CKD.[58,123] Thus, best practice would suggest following the guidelines of the National Cholesterol Education Program Adult Treatment Panel II for initial classification, treatment initiation, and target cholesterol levels for diet or drug therapy.[124] Finally, the Heart Protection Study suggested benefit in treating patients with coronary disease, other occlusive arterial disease, or diabetes largely irrespective of initial cholesterol concentrations.[125]

Diabetes Control (See Chapter 11)

Optimal diabetes management should be encouraged and facilitated with referral to a diabetes clinic if possible. Intensive glucose control in both types 1 and 2 diabetes may prevent or stabilize the early stages of microvascular complications, including CKD.[126,127] This impact seems to be sustainable for years, a so-called legacy effect.[128] However, intensive glycemic control has not been shown to slow progression of DKD in patients with macroalbuminuria or decreased kidney function. Furthermore, as kidney function deteriorates, management of hyperglycemia will require modification.

Lifestyle Modification

Smoking cessation is recommended for many reasons, including the possibility that it may slow loss of kidney function.[129,130] Obesity, poor diet, and sedentary lifestyle contribute to diabetes, hypertension, and vascular disease. Current recommendations are to achieve and maintain an ideal body mass index and moderate level of physical activity for 30 minutes per day for most days of the week.[92]

Rehabilitation

Cost of kidney disease from loss of work and associated loss of quality of life (QOL) is substantial. Strategies to enable patients to remain working or return to work should be in place and may involve referral to work retraining programs or occupational therapists, if available.[49,131]

PREPARATION FOR KIDNEY REPLACEMENT THERAPY

Individuals with progressive CKD require preparation for either kidney replacement therapy (dialysis or transplantation) or comprehensive clinical care. Creating and implementing these care plans is an iterative process that takes time and often requires input from several members of the healthcare team working with the individual. Home-based therapies that foster independent care are encouraged. The different modalities should be seen as complimentary, and individuals may transition through many modalities during their life. The appropriate timing of initiation of dialysis remains unclear, but it is certain that it must be individualized and must be based generally on a combination of low eGFR, patient symptoms, and other factors. Close follow-up of patients at the later stages of CKD, with objective assessment of global functioning, permits appropriate timing of dialysis initiation.

Modality Selection and Access Placement

Modality selection is a decision for the informed patient. It is unknown whether peritoneal dialysis or hemodialysis imparts a survival advantage over the other, as neither randomized trials have been done nor is one feasible in the future. Transplantation is a medically and economically superior treatment[132] for kidney replacement therapy and is associated with higher quality of life. At any given time approximately 50% to 60% of patients receiving dialysis are eligible for transplantation, but estimates are not available for those with earlier stages of CKD. Not all patients are eligible for transplantation, such as those with severe underlying illness. Preemptive transplantation, that is, before the need for dialysis, is generally possible for only those with an available live donor. In the United States, approximately 30% of transplants are from living donors, and one fifth of these are unrelated to the recipient.

It is clear that for some people, contraindications to one of the modalities may exist; for example, extensive prior abdominal surgery may negate the possibility of peritoneal dialysis. Importantly, the patient's desire to undertake chronic dialysis must be closely explored, because there may be some with serious underlying illnesses who choose to not undertake renal replacement therapy.

The options for kidney replacement therapy need to be reviewed with the patient, and vascular access should be planned appropriately, if needed. The reality of how long it takes to decide on a modality, have vascular access placed, and let the access mature should be stressed to patients. Also, the possibility that the first vascular access may not work should be discussed. A perspective on the relative amount of time required to prepare for each of the options, including transplantation, should be provided. It should also be stressed that the presence of a working access (such as a functioning fistula) does not mean the patient has to start dialysis earlier. A functioning, albeit unused, vascular access reduces the chance that additional procedures, such as placement of a temporary dialysis catheter, might be needed.

Lack of preparation for dialysis increases morbidity and cost.[133–135] Cost and morbidity implications of temporary catheter-based vascular access are extensive. They include the cost of catheters, insertion fees, radiology tests, costs associated with complications such as infection and thrombosis, and the pain, discomfort, and time of the patient.

Planning for kidney replacement therapy should begin at least 6 months in advance of the anticipated need to start. According to most published guidelines, vascular access

should be created the eGFR is approximately 20 to 25 ml/min/1.73 m^2 in those who are anticipated to progress and who do not have a reasonable chance for a preemptive transplant. Reasons for lack of access at the start of dialysis may include patient factors such as denial of inevitable dialysis, being too sick to undergo permanent access procedures, or late decision to undertake chronic dialysis. However, this may also reflect the CKD team's inability to predict the start of dialysis, lack of resources, or poor planning. Late recognition of CKD and late referral to nephrology contribute to the problem.

In consultation with the patients and the clinic team, optimal timing around education, decision-making, and access creation should be undertaken.

Timely Initiation

When to initiate dialysis is a complex decision that involves the consideration of many variables. There are some easily identified absolute indications for initiation;[136] however, debate exists with respect to "timely" dialysis when these indicators are not so apparent. Indeed, since the 1970s Bonomini[136–138] has argued for initiation of dialysis before clinically significant markers of uremia appear. His studies suggested a positive association between residual kidney function at dialysis initiation and clinical outcomes. Unfortunately, lead-time bias, patient selection, or referral bias may favor outcomes in the population of patients starting "timely" dialysis. Further complicating the issue is the lack of a tool to define where a patient is on the time line of CKD, for both planning and comparison of study results. To date, there is no solid evidence regarding how "early" dialysis should be started for optimizing patient outcomes.

Presently, two main indices for initiating dialysis for the treatment of kidney failure following progression of CKD are: 1) low eGFR, and 2) symptoms or signs of uremia, or evidence of malnutrition.[107] The 2006 National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines suggest that the benefits and risks of initiating renal replacement therapy should be considered in patients with an eGFR less than 15 ml/min/1.73 m^2 (stage 5 CKD).[139] Initiation of dialysis in patients prior to stage 5 CKD may be required in patients with certain complications of CKD. Despite these and other guidelines, when to initiate dialysis remains debatable and should be done after consideration of clinical symptoms, the totality of the metabolic and hormonal disturbances, and other patient factors. Reliance on eGFR values alone to determine initiation would not be prudent. Overall, the key factor is to avoid commencing dialysis when the patient is so ill that education opportunities and the chances for maintaining independence are impaired.

Hemodialysis

The goal is a nontraumatic start to hemodialysis care, and the CKD clinic staff should ensure the appropriate commencement of dialysis, including ensuring that patients have appropriate vascular access and are oriented to the hemodialysis unit. Schedules should be coordinated with appropriate team members in the hemodialysis unit, family members, and other medical professionals. The CKD clinic should send initial dialysis orders and transfer summaries to the hemodialysis unit.

Peritoneal Dialysis

Patients should be oriented to the peritoneal dialysis unit and staff. The role of the CKD clinic in organizing peritoneal dialysis catheter placement will vary from center to center. However, the timing, placement, and preliminary education should be done in concert with the peritoneal dialysis team. As in hemodialysis, specific orders and transfer summaries should be sent to the peritoneal dialysis unit and the training/initiating schedule coordinated with appropriate team members, family members, and other health professionals.

Transplant

As part of the educational process early in the course of CKD, the concepts of transplantation and living donation should be explored with patients and families. The CKD clinic working closely with the transplant assessment team can help determine eligibility for a transplant. Furthermore, a CKD clinic can facilitate preemptive transplantation, which is generally only possible if the patient with CKD has an available live donor.

Comprehensive Conservative Care

Not all patients will desire, or benefit from, kidney replacement therapy; longer-term education, longer follow-up time, and an established relationship with CKD team members will facilitate making this choice. In these cases, the CKD clinic staff may be the first to be aware of the wishes of the patients and families, and other caregivers should be informed of these decisions. If appropriate, consultation with psychiatry may be helpful to ensure the patient has a sound state of mind and the ability to weigh the risks and benefits of the choices. Once the decision to decline renal replacement therapy is made, end-of-life wishes should be formalized, in particular extent of resuscitation attempts, with appropriate consent and documentation. Resources to ensure appropriate supportive care short of dialysis should be mobilized, because much can be done to maintain a patient who chooses to not undertake chronic dialysis. The patient should have referral for home care and for palliative care when appropriate. Patients may benefit from remaining in the care of the CKD team as plans of care may require revision or the patient may change his or her mind. Integration of the different teams may offer the best approach to ensuring optimal outcomes.

CLINIC LOGISTICS

Services

CKD clinics presumably exist within a healthcare system and society where the common goal is promoting health of the patients. Comprehensive care delivered in only one location is presumed to be beneficial. The frequency with which

any individual patient accesses care is determined by the specific circumstances of the medical system, the other physicians involved in patient care, additional comorbid conditions, and the specific stage of disease. The clinic should provide a wide range of services for patients with kidney disease, and their physicians, with the overall goals of:

1. Ensuring patient and family understanding of kidney disease
2. Ensuring understanding of healthcare system or hospital and outpatient systems and services available to patients with CKD
3. Identifying potential issues related to long-term patient management
4. Facilitating longitudinal and parallel care of patients with CKD

Key Components of the Clinic

The clinic should ideally be an outpatient facility providing easy access to all facilities and personnel in one location. This permits familiarity with team members and access to ancillary services as needed. If also located in proximity to the hospital or dialysis center, it provides familiarity with the respective hospital services and locations. If the patient does not speak the primary language of the clinic, translation is essential. Ideally, translation should be provided by a medical interpreter provided by the healthcare facility to ensure unbiased translation. If this is not available, the patient should be encouraged to bring friends or family members that speak the primary language of the clinic. An information package should be available and given out at the first visit, including an introduction to how the clinic works and various educational materials such as goals and expectations. Patients and families should also have an introduction to team members and an explanation of the roles and responsibilities of each team member. Finally, the clinic should facilitate peer support for patients with CKD.

In addition to ongoing assessment of patient by the team through regular clinic visits, weekly multidisciplinary rounds should be organized to facilitate communication and develop or adjust plan of care. This will allow for comprehensive follow-up by nurses, clerical staff, and others and will facilitate:

- Bookings for tests (ultrasound, computerized tomography, etc.) and referrals to other specialists
- Medication changes, tolerance, and so on
- Reminders for appointments and blood work
- Follow-up of test results
- Liaison with laboratories and pharmacies
- Liaison with primary care providers and other consultants, including palliative care team (in hospital or community)
- Patients should receive education about kidney or kidney/pancreas transplant and screening for potential donors and referrals as appropriate

Individual Roles

For a team to function, definition and clarification of roles of the individuals involved are important. The following section lists key roles and responsibilities for each of the key staff deemed important in the delivery of CKD care. The specifics may vary depending on local issues, but the principal roles need to be clearly defined.

Nurse

The CKD nurses functions as a case manager and facilitates care of patients, both directly and through physician and team member liaison. Nursing support should be available by telephone or in person to triage medical concerns, answer questions, and provide education or emotional support and referral to other team members or community resources. This should allow for ongoing collaboration and reevaluation with the patient, and should facilitate changes in care plan with input from team members. A regular review of symptoms, medications, and monitoring of lab work results should occur, again responding to critical values by notifying physician, patient, and dietitian as necessary. The nurse should be able to liaise with family physicians and other primary care providers, consultants, and other chronic disease clinics (e.g., diabetes, heart health clinic).

Nurses should be able to implement protocols such as hepatitis screening and vaccination program or periangiogram protocols. Similarly, they should be able to arrange treatments and procedures such as intravenous iron and transfusions and arrange referrals for dialysis access and follow-up care. If patients progress to kidney failure, then the nurse should ensure coordination of initiation of dialysis or referral for transplantation and transfer of relevant data to dialysis or transplant facility. Finally, they should coordinate services in remote settings for the convenience of patients.

Dietitian

Patients should receive individualized diet education and counseling regarding CKD, diabetes, and heart disease from a dietitian knowledgeable about the nutritional abnormalities of CKD. The dietitian should review diet history, habits, and nutritional health, and should advise patient about food choices and meal ideas. There should be a periodic dietary review, including blood work, to help reach goals and maintain good nutrition.

Social Worker

Social workers may provide assistance with emotional and practical concerns of patients and their families and may assess emotional needs or potential issues that may arise, such as acceptance of kidney failure and end-of-life issues. The social worker should have a mechanism to liaise with psychiatry support as needed. They also advocate on the patient's behalf to ensure maximum allowable benefit from available resources such as home support, financial assistance, employment and retraining, and housing, and they may need to assist the patient with insurance issues, including referral to institutional financial counselors.

Pharmacist

If possible, pharmacy services should be available for initial medication review and follow-up. They may advise about medication costs, pill burden, and possible drug

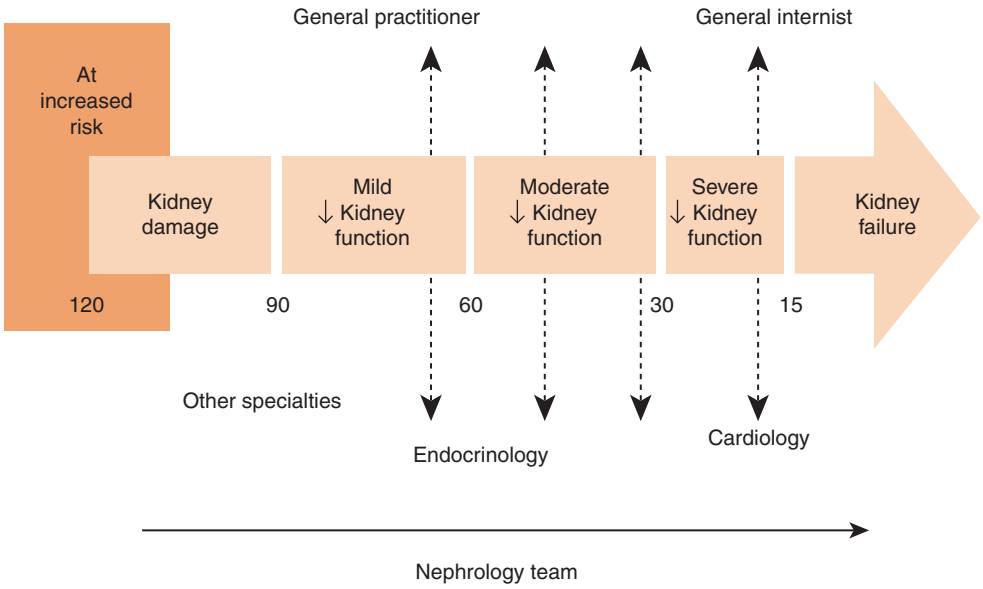


FIGURE 6-2 Integration of care over the progression of CKD (Longitudinal Care) and between other caregivers (Parallel Care).

interactions. They may also provide education and support as needed.

Clerical or Administrative Support

Clinics should have a dedicated unit coordinator or clerical support worker. This person's main role is to ensure that data and patient charts are maintained accurately. A paper or electronic chart should be established with complete information available and maintained with ongoing follow-up data. This will include data such as labs, medications, and comorbidities. The coordinator is an essential component of the team as the organization of booking and coordinating appointments with other clinics, consultants, diagnostics, and community resources and follow-up is essential. Additionally, they are integral for information and chart transfer to programs within the kidney programs such as dialysis or transplant clinic. They may also triage patient concerns with the team and have appointment reminders for patients. Finally, they should identify interpreter requests and book interpreters as needed.

Chronic Kidney Disease Clinic Role in Longitudinal Care: Different Stages of Chronic Kidney Disease

Given the current estimates of the CKD population (between 10 and 20 million in the United States), it is unlikely that the optimal resources described in this chapter are available to all patients with CKD. It is still debated whether a nephrologist must see all patients with early CKD, as it is not clear who will and who will not progress. Although there is consensus that nephrologists and teams need to see the patients at least 6 months, and ideally 12 months, prior to dialysis start for access, there remains skepticism regarding the use of nephrology input prior to that time.

Although much has been learned about care of patients close to initiating dialysis, it is not known how to optimally care for patients in early CKD (frequency of visits, frequency of blood work, when to initiate "early" drug therapy, etc.). It seems reasonable that a "phased" approach is applicable. As outlined, the focus of the clinic must be adjustable from early disease detection and risk factor modification to preparing for kidney replacement therapy. Key at all phases would be communication and education between patients, medical caregivers, and allied health teams (Figure 6-2).

One end of the spectrum is an early referral (stage 1 or 2) and a broad plan outlined to another caregiver about goals of treatment for that caregiver to follow. Patients could be familiarized with the clinic and kidney disease at this initial period and then referred back to the clinic if the kidney function deteriorates for further education and refinement of management plan. Both the patient and the other caregiver are informed that the clinic is available when needed for either informal consultation or formal evaluation. The other end of the spectrum is for the clinic to assume most of the care, if not all, surrounding issues pertaining to kidney disease and other issues such as diabetes management. In between, the clinic could do a formal initial evaluation and then arrange follow-up once every year or so. To date there are no studies that have systematically evaluated the impact of different methods of care at earlier stages of CKD.

Chronic Kidney Disease Clinic Role in Parallel Care: Integrating with Other Caregivers

An important issue in dealing with individual patients who are obtaining care in parallel locations (i.e., family physicians, diabetes services, and CKD clinic) is communication. The clinic should be viewed as a resource to both patients and parallel caregivers such as family physicians and other primary care providers, and as such, could integrate care with other caregivers. For example, other caregivers could call to seek advice regarding safety of medications, and the clinic can serve as a facility to follow the patients during acute events (e.g., increased creatinine around diarrhea and temporarily holding

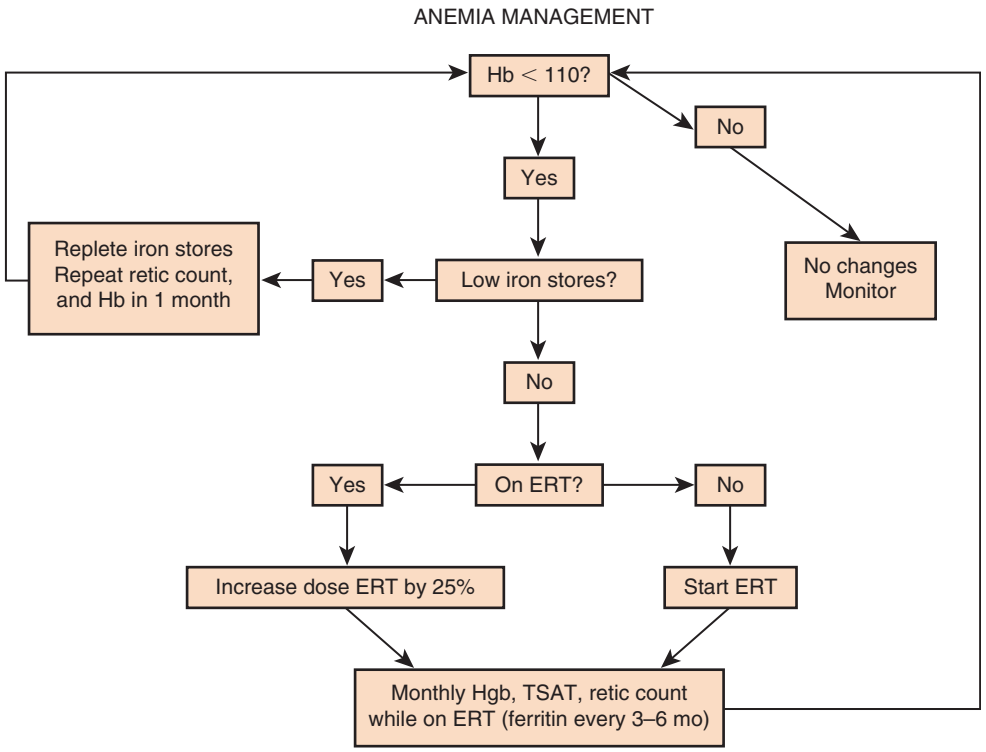


FIGURE 6-3 An example of a protocol for anemia management that may guide therapy by physician or specialized nurse. It assumes all secondary causes of anemia have been ruled out. ERT, erythropoietin replacement therapy (erythropoietin or darbepoetin); Hb, hemoglobin.

the ACE inhibitor). It is vital for such a clinic to communicate information about patient status, medications, plans, and so forth, not only to the patient but to all other caregivers involved (family physicians, diabetes clinics, hospital charts).

When inpatients access different care systems due to the complex nature of their disease or due to practical issues such as locale, it is not so clear how to determine the responsibility of each of the individual medical practitioners. Should the CKD clinic assume the ACE inhibitor is being managed by the heart health clinic? Or does the CKD clinic assume the diabetes clinic is managing the blood sugar control or counseling about smoking cessation? At what point in the stage of CKD does the CKD clinic take a more active role? These are not questions that will be answered in clinical trials, so practical solutions to the issue of responsibility for care implementation will need to be developed. Again the key issue here is the communication between different physician groups and medical teams and customization to individual patient and healthcare system particulars. There is an accumulating body of literature[53–58] that suggests involvement of the patient in all implementation plans and knowledge of and active involvement in therapy targets and test results improve the ability of physicians and other health care professionals to implement care strategies.

Other Benefits of the Chronic Kidney Disease Clinic and Organized Protocolized Care

The key to the care of patients with chronic diseases is acknowledgment of the complexity of the condition(s) and the need for longitudinal follow-up by a well-trained team. As in other areas of medicine, the care of patients with CKD requires some adoption of protocols for investigation, therapy, and follow-up (Figure 6-3 and Table 6-3). In so doing, we will be able to develop sensible strategies based on data, and management of selected conditions will be uniformly undertaken. The systematic evaluation and management of patients with chronic diseases has been demonstrated to reduce resource use and to enhance patient compliance.

The additional advantages to the clinic models for the care of CKD include the ability to optimize all aspects of care by using individual team member's expertise more appropriately and to optimize follow-up and monitoring of large groups of patients in one area. Furthermore, a clinic-based approach allows database development and evaluation of outcomes in large cohorts of patients, the ability to enroll patients in clinical trials, and importantly, the adoption of newer proven

TABLE 6-3 Example of a Protocol for Follow-Up/Blood Work Intervals*Minimum Follow-Up/Bloodwork Intervals as a Function of Kidney Function

CREATININE CLEARANCE (ml/min/1.73 m²)	INTERVAL BETWEEN VISITS/ BLOODWORK	
	DIABETICS	*NONDIABETICS*
31–60	3 months	3 months
15–30	2 months	3 months
10–14	1 month	2 months
<10	1 month	1 month

*Maximum intervals (or minimum frequency) between visits are given for stable patients. Shorter intervals may be necessary at discretion of physician or specialized nurse in less stable patients, or be specified in therapy titration algorithms (e.g., initiation of erythropoietin replacement therapy).

therapies may be easier in a clinic setting than in individual physician offices.

The clinic structure may also ensure that patients have access to appropriate current information and materials that may not be available in individual physician offices. Also, it will permit coordination of care plans and execution of those plans within health system structures.

Barriers to care or implementation of strategies can be identified in a clinic setting. The costs and the number of medications required for CKD is becoming progressively daunting and leads to problems with compliance. These problems are more likely to be identified within a clinic setting, where social workers, pharmacists, and others may more readily identify issues not necessarily identified by physicians. The importance of an asymptomatic condition can be reinforced in clinic settings where the patientteam interaction is far longer than the usual patientdoctor visit.[47] Although there may be multiple problems and barriers that interfere with achieving care goals in an individual, an organized team approach is more likely to identify those barriers in a timely manner.

RECENT AND FUTURE STUDIES

The CAN-CARE (Canadian Care Prior to Dialysis) study [140] is a prospective multicenter cohort study of incident patients with an eGFR less than 50 ml/min/1.73 m^2 referred to nephrologists across Canada. Enrollment began November 2000 and the study ended in 2004. The objectives were to describe: 1) the specific care ("elements") these patients receive over time, 2) the prevalence of cardio renal risk factors at referral and at 12 and 24 months, and 3) the link between specific elements of care and outcomes/quality of life. Despite increasing awareness of CKD care objectives and a universal health care system, the care across Canada remains variable. The availability of formal clinics is not standardized, and the accessibility of specific resources for CKD patients is not uniform across the country. Nonetheless, the study demonstrated that in 2000, referral to nephrology remained relatively late, with the mean referral eGFR of approximately 23 ml/min/1.73 m^2. Nephrologists tend to focus on anemia and blood pressure in the first year of follow-up. The outcomes of those referred to nephrologists appears to be different than those described in population-based studies in that there is a greater likelihood of commencing dialysis than of dying. In a large cohort of patients in British Columbia, Canada,[141] we described a similar phenomenon. Importantly, those factors that lead to more rapid progression of a referred population include younger age, male gender, proteinuria, hemoglobin levels, and serum phosphate levels. Some of these factors remain amenable to interventions, but have not yet been rigorously studied in randomized control trials.

The Study of Treatment for Renal Insufficiency: Data and Evaluation (STRIDE) registry will study data on prevalent CKD patients in nephrology practices in the United States.[142] The Chronic Renal Insufficiency Cohort (CRIC) study will examine risk factors for progression of CKD and CVD among those patients. The main goal is to develop models identifying high-risk subgroups and, subsequently, increase application of preventive therapies.[143] The Kidney Early Evaluation Program (KEEP) was implemented to increase awareness of kidney disease among those at highest risk and, subsequently, to improve outcomes through early detection and referral for care. The KEEP 2.0 screening program identified persons with reduced kidney function and suboptimal care. The KEEP 3.0 will continue to identify individuals at high risk for kidney disease and will address educational needs by randomly assigning participants to one of several educational programs.[144]

The Can-Prevent trial is a Canada-wide multicenter clinical trial to address the hypothesis that compared to usual care, a nurse supported by a nephrologist, running a multiple risk factor intervention and disease management clinic for people with moderate CKD identified by laboratory-based case-finding, will reduce or delay the onset of advanced kidney disease, cardiovascular events, and death. The study assessed the effect on health care resource use, costs, and QOL. Measurements of QOL in patients with kidney disease have demonstrated worsening QOL as a function of anemia and need for dialysis. A systematic study of QOL prior to dialysis has not been undertaken, because there is a lack of organized access to this group of patients. The study is closed as of the writing of this chapter, but has not yet been reported. Of note, the laboratory case finding strategy employed in this study resulted in a substantial number of patients being enrolled with relatively well-preserved kidney function.

Currently, more well-designed studies are needed to better understand the impact of various therapeutic regimens on patient perceptions of health and wellness. Furthermore, it is imperative that we better understand the impact of various aspects of the professional care delivered (e.g., time spent, education provided) and assess the association of these with outcome. The use of specific interventions, alone or in combinations, also needs to be better understood in various stages of disease or subpopulations. Thus, there is still much to study about the optimization of care of CKD.

CONCLUSION

Kidney disease involves the complex physical, mental, and social aspects of health mandating an understanding and rational use of available resources. Opportunities exist to improve early identification and follow-up of patients with CKD and to ensure better outcomes overall, regardless of whether patients ultimately require dialysis.

To focus on these complex aspects of care, the inclusion of medical, nursing, dietary, social work, and pharmacy staff in a coordinated system, with protocolized goals and systematic approaches to longitudinal follow-up is required. It is hoped that the information supplied herein will help develop templates and deliveries of care models for further evaluation, so that, ultimately, the outcomes of patients with CKD at all stages of disease are improved.

A full list of references are available at www.expertconsult.com.

Chapter 7

ANEMIA IN CHRONIC KIDNEY DISEASE

Steven M. Brunelli, M.D., M.S.C.E., and Jeffrey S. Berns, M.D.

Anemia, a reduction in blood hemoglobin (Hgb) concentration or hematocrit (Hct), is common among patients with chronic kidney disease (CKD). Evidence indicates an incremental and monotonic increase in the prevalence of anemia with reduced glomerular filtration rate (GFR) (Figure 7-1),[1–3] which stems primarily from a reduction in endogenous erythropoietin production by the kidneys. Using the World Health Organization definition of anemia as an Hgb concentration below 13.0 g/dl for adult males and postmenopausal women, and an Hgb below 12.0 g/dl for premenopausal women,[4] as many as 90% of patients with CKD and a GFR less than 30 ml/min have anemia, and many have Hgb levels below 10 g/dl.[5]

The prevalence of anemia in any population sample with CKD varies depending on the level of GFR and definition of anemia. In general population studies, the prevalence of anemia defined as an Hgb less than 11 g/dl was approximately 1.3%, 5.2%, and 44.1% among patients with estimated GFR (eGFR) rates of 60 to 89, 30 to 59, and 15 to 29 ml/min/1.73 m^2, respectively.[6] Historically, consideration of, and therapy for, anemia in CKD were largely limited to patients with end-stage renal disease (ESRD) and very severe anemia. In recent years, there has been a paradigm shift toward anemia therapy earlier in the course of CKD, driven by recognition of the high and rising prevalence of CKD and its complications[7,8] and the presumption of the beneficial effects of early intervention. This has resulted in a reduction in the prevalence and severity of anemia among patients with CKD who are not on dialysis, and a trend towards higher Hgb levels among patients initiating renal replacement therapy.

A low Hgb concentration reduces the oxygen carrying capacity of blood, which in turn reduces tissue oxygenation delivery, and necessitates a compensatory rise in cardiac output. The combination of these factors may adversely affect health and well-being and predispose the patient to increased morbidity and mortality. There has been a proliferation of research seeking to define the effects of anemia therapy among patients with CKD and to identify therapeutic goals that maximize health outcomes.

In this chapter, we will discuss in turn: 1) the pathogenesis of anemia in CKD, 2) the clinical consequences of anemia and its therapy, 3) existing therapies, 4) recommended therapeutic goals, 5) erythropoiesis stimulating agent (ESA) hyporesponsiveness, and 5) emerging and controversial issues in anemia management in CKD.

PATHOGENESIS

Anemia in CKD is characterized by a normochromic normocytic appearance of peripheral circulating erythrocytes without the expected increase in bone marrow and progenitor cells and circulating reticulocytes one would expect with the observed low Hgb concentration. The anemia associated with CKD derives principally from inadequate production of the hormone erythropoietin by the kidneys.[9] Identification and purification of erythropoietin and cloning of the erythropoietin gene led to the production of recombinant erythropoietin

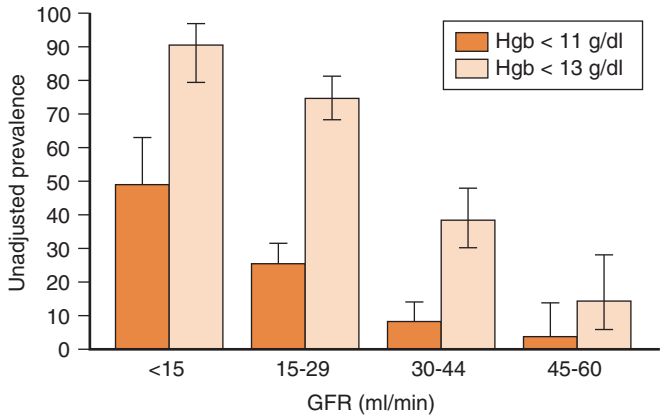


FIGURE 7-1 Prevalence of anemia among untreated patients with chronic kidney disease according to degree of residual renal function. (National Kidney Foundation. *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am. J. Kidney Dis. *2002* 39 (2 Suppl 1) S1-S266.

hormone;[10–12] therapeutic administration of this agent confirmed the primacy of erythropoietin in the pathogenesis of the anemia of CKD.[13,14] Impairment of the erythropoietic response to endogenous or exogenous erythropoietin due to the "uremic milieu" may also contribute to the anemia of CKD, with various polyamines, parathyroid hormone, and inflammatory cytokines such as interferon-γ and tumor necrosis factor-α being other potential inhibitors of erythropoiesis.[15–17] Major features of the pathogenesis of CKD-related anemia are depicted in Figure 7-2.

Erythropoietin is a circulating glycoprotein of 165 amino acids with three N-linked and one O-linked carbohydrate chains. Prenatally the hormone is produced in the liver, and postnatally it is synthesized primarily by peritubular interstitial cells in the kidneys.[18,19] Erythropoietin is present in the circulation in low concentrations (0.01 to 0.03 units/ml) under basal conditions, but the concentration increases 100- to 1000-fold in response to hypoxia and anemia,[20] in a process regulated by hypoxia-inducible factor-1(HIF-1).[21,22] HIF-1 is a transcription factor that binds to a hypoxia response element in the erythropoietin gene and other hypoxia-responsive genes, increasing their transcription; expression of the HIF-1α subunit of the HIF-1 complex increases rapidly in response to hypoxia while in the presence of oxygen, HIF-1α rapidly undergoes proteosomal degradation following ubiquitination by the von Hippel-Lindau protein complex.[23,24]

Erythropoietin receptors are present on erythroid precursors, with the greatest expression on colony forming unit-erythroid cells;[25] stimulation by erythropoietin induces their proliferation and maturation into mature erythrocytes. Erythropoietin receptors are not found on mature red blood cells but are present on some nonerythroid cells such as the endothelium, kidney, brain, and heart. The erythropoietin receptor is a preformed dimer. Binding of erythropoietin to the receptor changes its conformation, leading to activation of the intracellular mediator kinase Janus kinase-2 via transphosphorylation, subsequent phosphorylation of other intracellular tyrosine kinases, and stimulation of a complex signal transduction cascade that eventuates in erythrocyte production.[26–28]

Erythropoietin deficiency and the anemia of CKD may be preceded or exacerbated by states of absolute or functional iron deficiency; these will be discussed in detail later in the chapter. Additionally, CKD patients may have anemia on

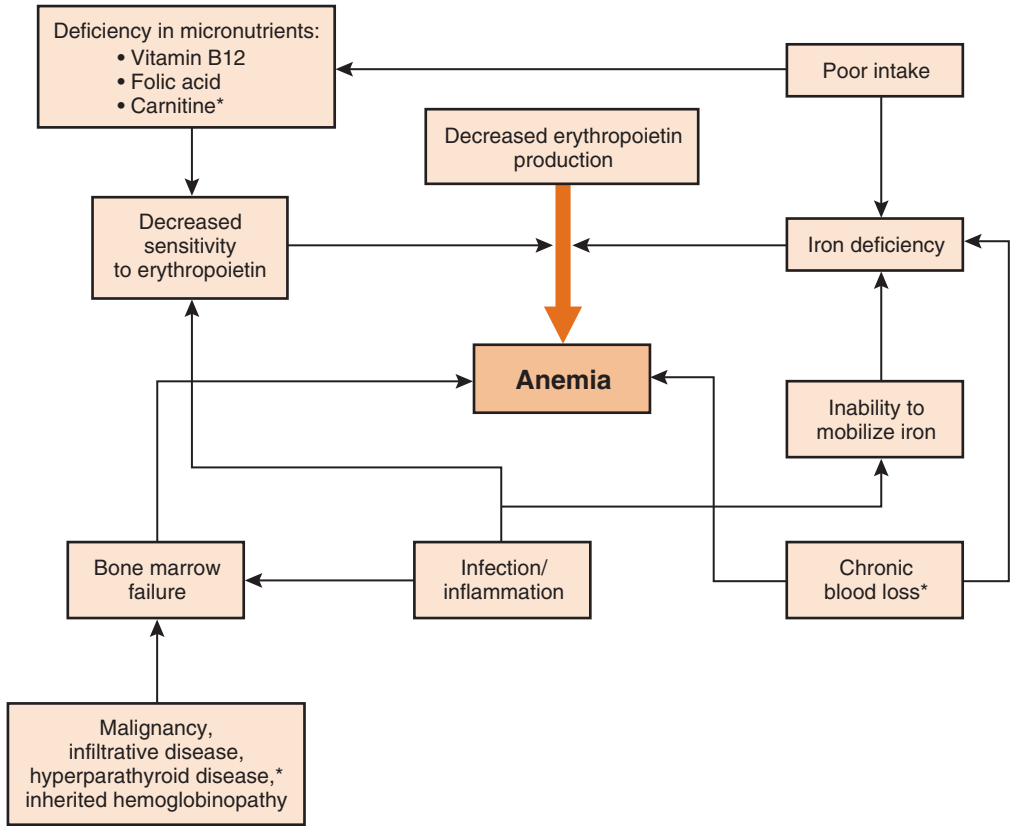


FIGURE 7–2 Mechanisms for the development of anemia in patients with CKD. *Indicates factors more relevant to hemodialysis patients.

the basis of other conditions, such as vitamin B_{12} or folate deficiency, bleeding, hemolysis, infection or inflammation, bone marrow infiltration, inherited hemoglobinopathies, and medication side effects (particularly angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]).[29,30] Among patients on chronic hemodialysis, other factors include influence of blood loss via the dialytic circuit, subclinical access infection (particularly with senescent arteriovenous synthetic bridge grafts), secondary hyperparathyroidism, and inadequate dialytic solute clearance.[17,31]

CLINICAL CONSEQUENCES OF ANEMIA AND EFFECTS OF CORRECTION

Health-Related Quality of Life

The symptoms of anemia are nonspecific and can overlap with those of advanced kidney failure and uremia. They include fatigue, shortness of breath and dyspnea on exertion, impaired exercise tolerance, difficulty concentrating, headaches, lightheadedness, impaired sexual function, and diminished sense of well-being. Many studies using recombinant human erythropoietin in both patients on dialysis and patients with CKD not on dialysis have documented that health-related quality of life (HRQoL) improves in association with partial correction from severe to more moderate degrees of anemia.[32–38]

In more recent years, there has been renewed interest in this area, particularly as the potential benefits and risks of using erythropoietic stimulating agents (ESAs; a general term that will be used in this chapter to refer to recombinant human erythropoietin and other similar or related pharmacological preparations) to raise Hgb levels closer to normal have been examined. Improvement in various HRQoL parameters, such as physical function, energy and fatigue, school performance in children, vitality, and reduction in hospitalization rates have been well documented in randomized controlled trials and in observational cohort and other studies (Figure 7-3).[39–44] On the other hand, one large, randomized study failed to demonstrate a benefit of anemia correction on HRQoL,[45] although methodological issues may have limited this study's ability to assess HRQoL as an endpoint.[46] Another more recent larger placebo controlled trial of darbepoetin in patients with CKD found modest improvement in patient reported fatigue but not other quality of life measures. Most of these studies have been of short duration, and the long-term persistence of HRQoL benefits occurring in response to anemia in CKD patients remains unknown. Uncertainty in this regard led the U.S. Food and Drug Administration (FDA) to revise the product labeling to remove claims that ESAs improve patients' quality of life, symptoms of anemia, fatigue, and general well-being.[47]

Cognitive Function

Decreased oxygen delivery to the central nervous system is expected to result in impairment in cognitive function, an effect that should be amenable through anemia correction. A number of randomized trials have demonstrated a favorable effect of anemia treatment on cognitive function in dialysis patients. In this population, full[48] and partial[49] anemia correction have been demonstrated to improve performance on neuropsychiatric testing and electrophysiological markers of cognitive function. Additional evidence suggests that complete normalization of Hgb is superior to partial correction in this regard,[50] an effect that must be weighed against potential detrimental effects of Hgb normalization (discussed later). Partial anemia correction has also been associated with improvement in intelligence quotient, concentration, memory, and speed of information processing,[51] as well as improvements in sleep quality and wakefulness.[52]

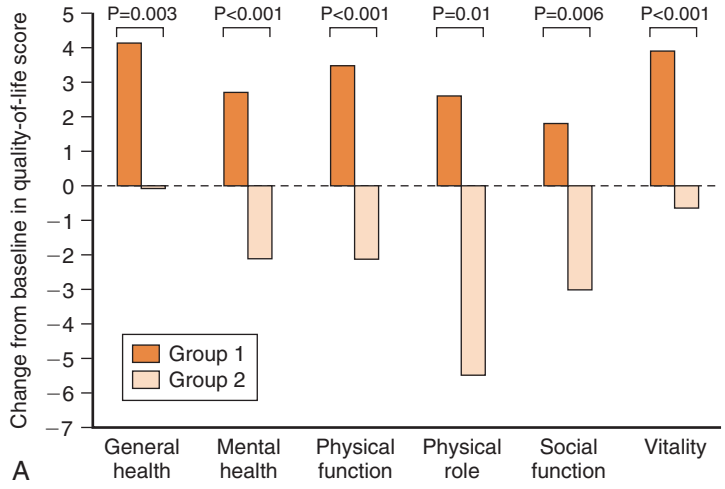
To date, little work has been done to examine the cognitive effects of anemia correction among patients with earlier stages of CKD who are not on dialysis. One study demonstrated that anemia correction results in improvement in electrophysiological markers of cognitive function,[53] but none has examined clinical outcomes such as neuropsychiatric testing. Given the lesser severity of anemia in the milder stages of CKD and inherent differences in comorbidities compared to patients on dialysis, it is unclear whether extrapolation of data from dialysis patients is warranted. Thus, for CKD patients who are not on dialysis, provision of anemia therapy with the intent of achieving improvement in cognitive function is probably not warranted unless further evidence becomes available.

Cardiovascular Disease and Mortality

As Hgb concentration falls, there is a commensurate reduction in blood oxygen carrying capacity (Figure 7-4).[54] To maintain constant tissue oxygen delivery, cardiac output is increased via augmentation of heart rate and stroke volume. As part of the compensatory process, left ventricular geometry is altered, with increases in left ventricular end-diastolic volume and wall thickness. In addition, data in experimental models suggest that anemia induces changes in cardiac myosin expression, favoring more active isotypes.[55]

Left ventricular hypertrophy is common among patients with CKD,[56] and its prevalence is strongly associated with the degree of anemia present.[57] In this population, left ventricular hypertrophy is a potent marker for cardiovascular morbidity and mortality.[58] Therefore, it is not surprising that observational data suggest an association between greater degrees of anemia and increased risk of myocardial infarction, stroke, and death among patients with CKD.[59] These observations have led some to hypothesize that anemia correction would result in both an improvement in left ventricular geometry (e.g., decreased hypertrophy) and better cardiovascular outcomes (e.g., fewer myocardial infarctions, strokes, etc.).

Most studies have demonstrated a beneficial effect of partial anemia correction on cardiac structural markers among patients with CKD not on dialysis.[60–63] In this population, anemia therapy has been shown to induce regression in left ventricular hypertrophy, and echocardiographic evidence of favorable left ventricular remodeling. Evidence suggests that complete correction of anemia does not provide benefit beyond partial correction in this regard.[40,64,65] Similarly, several studies have failed to



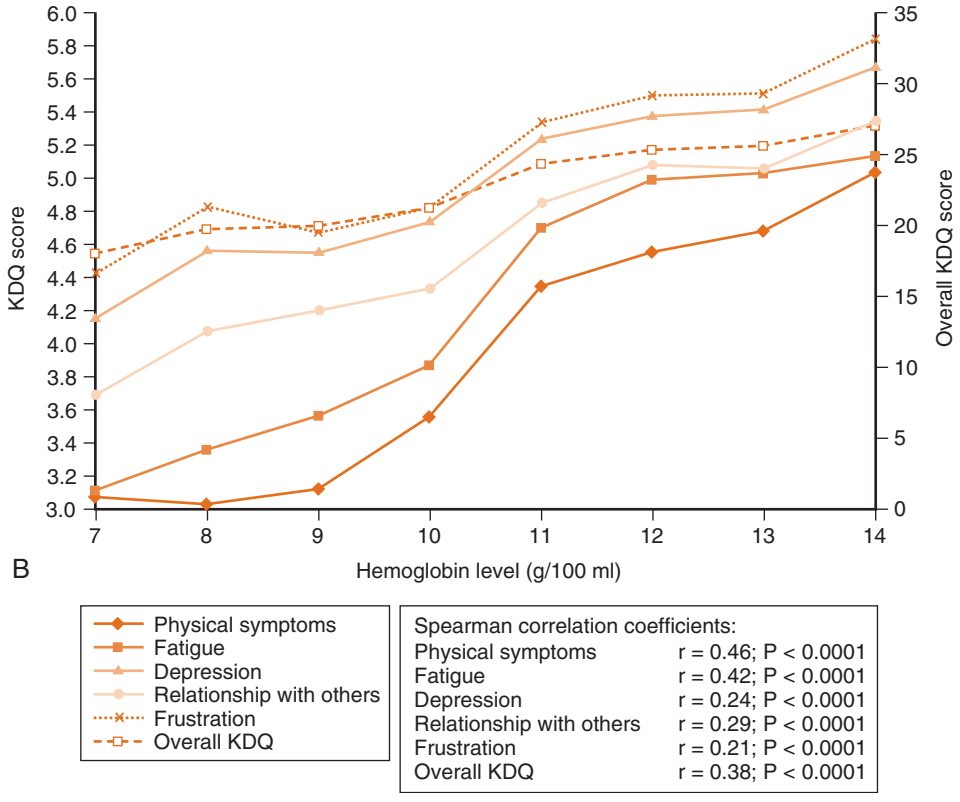


FIGURE 7-3 HRQoL in response to anemia correction in CKD. **A,** The change in SF-36 Health-Related Quality of Life domains among patients randomized to full (group 1) versus partial (group 2) anemia therapy in the CREATE study. **B,** The relationship between achieved Hgb level and components of kidney disease–related QoL scores. (**A** from T.B. Drueke, F. Locatelli, N. Clyne, et al., Normalization of hemoglobin level in patients with chronic kidney disease and anemia, N. Engl. J. Med. 355 [2006] 2071–2084. **B** reproduced with permission from P. Lefebvre, F. Vekeman, B. Sarokhan, et al., Relationship between hemoglobin level and quality of life in anemic patients with chronic kidney disease receiving epoetin alfa, Curr. Med. Res. Opin. 22 [2006] 1929–1937.)

demonstrate a beneficial effect of normalization or near-normalization of anemia therapy on clinical cardiovascular outcomes including cardiovascular mortality, myocardial infarction, stroke, need for cardiovascular intervention, hospitalization due to cardiac causes, or worsening heart failure among hemodialysis patients and CKD patients not on dialysis.[40,45,46a,65,66] In CKD patients not on dialysis, one trial demonstrated a statistically significant increase in the study's composite endpoint of hospitalization for congestive heart failure, myocardial infarction, stroke, or death,[45] and in another trial there was a trend, although not statistically significant, toward greater occurrence of a composite endpoint of sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina, peripheral vascular disease with amputation or necrosis, and arrhythmia (Figure 7-5).[40] In a recent placebo controlled trial of darbepoeting with a target Hgb of 13.0 g/dl, there was no reduction in the risk of a death or cardiovascular event outcome and an increased risk of stroke.[46a] A similar trial in dialysis patients failed to demonstrate cardiovascular benefit of Hgb normalization versus partial anemia correction.[66,67] It bears note that none of these trials randomized patients to placebo (all compared full to partial anemia correction), thus leaving in question whether anemia therapy, either full or partial, has cardiovascular benefits relative to no treatment.

A number of studies have examined whether anemia therapy improves survival among patients with CKD.

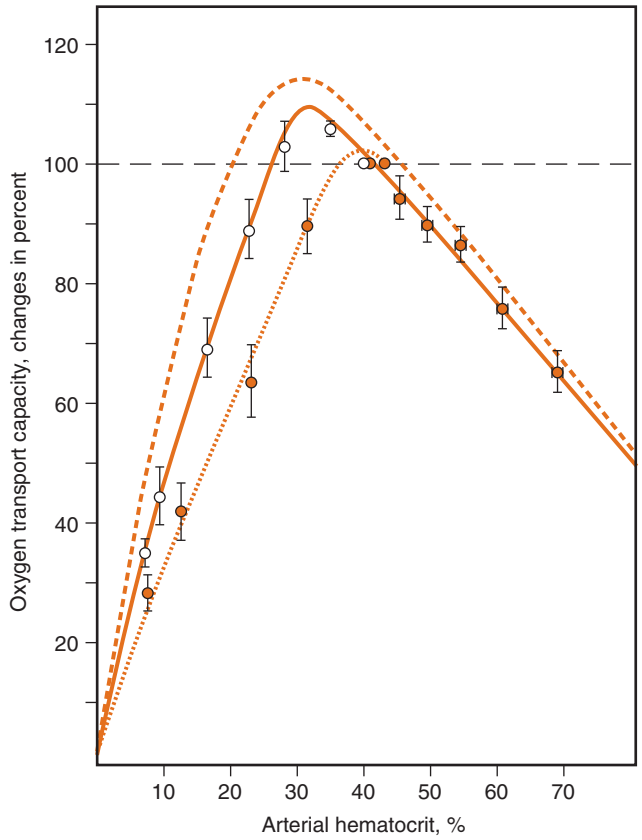


FIGURE 7-4 Relationship between Hgb content and blood oxygen carrying capacity. (Adapted from O.P. Habler, K.F. Messmer, The physiology of oxygen transport, Transfus. Sci. 18 [1997] 425–435, with permission from Elsevier.)

Among patients with CKD who are not on dialysis, observational studies suggest that higher Hgb levels are associated with improved survival,[59,68] and that anemia therapy is associated with improved longevity among patients going on to require dialysis.[69,70] However, Hgb levels are likely to reflect underlying health status, suggesting that these findings may be confounded. Three large randomized trials,[40,45,46a] and other smaller studies, failed to demonstrate any mortality benefit of full versus partial anemia therapy among patients with CKD; in fact, two of these larger studies suggested a nonsignificant trend toward higher mortality among patients randomized to full anemia correction (Figure 7-6).

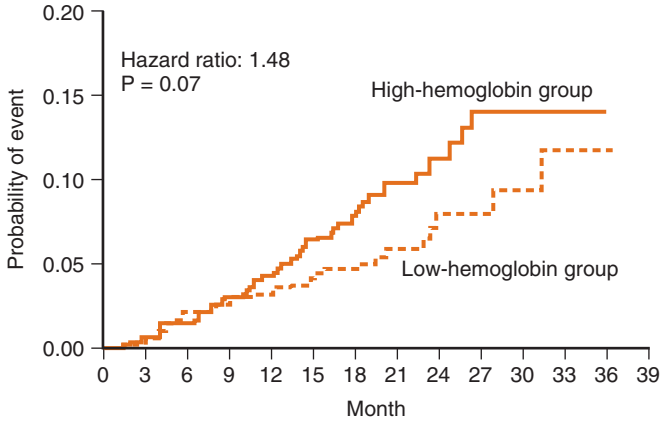
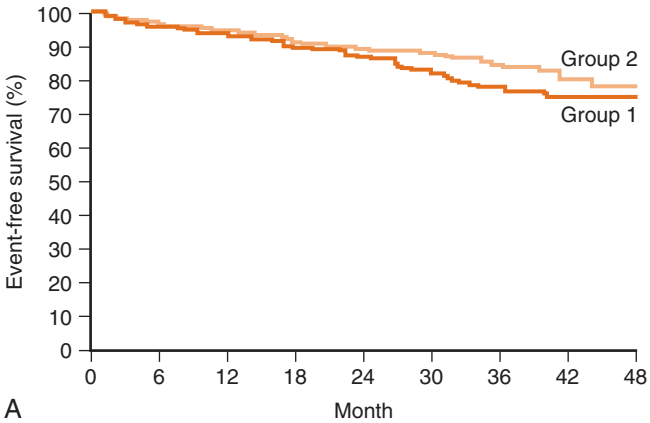


FIGURE 7-6 Effects of full versus partial anemia correction on all-cause mortality among patients with predialysis CKD. (From A.K. Singh, L. Szczech, K.L. Tang, et al., Correction of anemia with epoetin alfa in chronic kidney disease, N. Engl. J. Med. 355 [2006] 2085–2098.)

Observational studies examining the association between higher Hgb levels and mortality among patients on hemodialysis have yielded mixed findings, with some demonstrating a benefit,[71–75] and others not.[42,76,77] In the largest randomized controlled trial to date, full (versus partial) anemia correction was associated with a trend toward *increased* mortality.[66,67] Although this effect did not reach conventional levels of statistical significance, the concerning trend (seen on interim analysis) led investigators to stop the trial early, which may have reduced statistical power to detect statistically significant differences in mortality and other endpoints. Nonetheless, systematic reviews and updated clinical practice guidelines have cautioned against the normalization of Hgb levels with ESA treatment in dialysis and nondialysis CKD patients.[1,78–80]



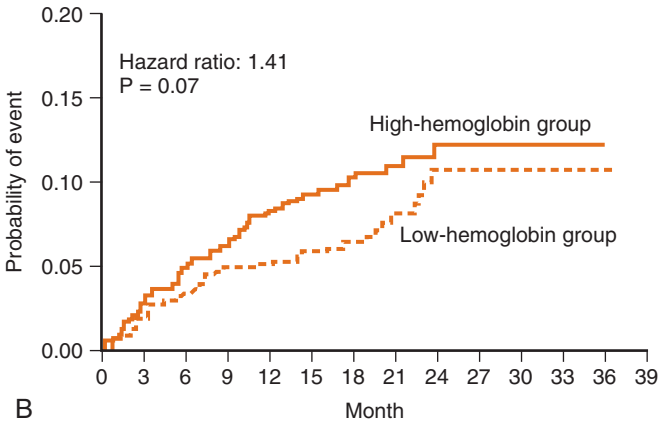


FIGURE 7-5 Effects of full versus partial anemia correction among patients with predialysis CKD. **A,** The Kaplan Meier survivor function for first cardiac event among patients randomized to full (group 1) versus partial (group 2) anemia therapy in the CREATE study ($p = 0.20$). **B,** The cumulative incidence of hospitalization for congestive heart failure among patients in the CHOIR study. (**A** from T.B. Drueke, F. Locatelli, N. Clyne, et al., Normalization of hemoglobin level in patients with chronic kidney disease and anemia, N. Engl. J. Med. 355 [2006] 2071–2084. **B** from A.K. Singh, L. Szczech, K.L. Tang, et al., Correction of anemia with epoetin alfa in chronic kidney disease, N. Engl. J. Med. 355 [2006] 2085–2098.)

THERAPIES FOR CHRONIC KIDNEY DISEASE–RELATED ANEMIA

Erythropoiesis Stimulating Agents

Since the first descriptions of the use of recombinant human erythropoietin in hemodialysis patients in the late 1980s,[13,14,81] ESAs have been the mainstay of anemia therapy for anemia in adults and children with CKD, including those not on dialysis, on hemo- and peritoneal dialysis, and after renal transplantation. Many studies have demonstrated the efficacy of ESAs in raising blood Hgb concentration. Erythropoietin alpha was demonstrated to be superior to placebo in this regard among patients with CKD who were not on dialysis.[13,38,81–83] The efficacy of other, newer ESAs has largely been established via noninferiority trials relative to erythropoietin alpha.[84–87]

Currently available ESAs are a class of recombinant preparations of human erythropoietin or its structural analogs, although other types of agents are undergoing clinical trials[88–91] and studies using gene therapies have also been reported.[92–95] This class of medications includes erythropoietin alpha (Epogen, Eprex, Procrit), erythropoietin beta (NeoRecormon,), erythropoietin delta (Dynepo), darbepoetin alfa (Aranesp) and methoxy polyethylene glycolepoetin beta (Micera). The term "epoetin" is often used to refer to all recombinant human erythropoietins. Erythropoietin alpha, darbepoetin alfa and methoxy polyethylene glycolepoetin beta have been approved for use in the United States, although the latter agent is not currently marketed in the United States. Unlike epoetins alfa and beta and darbepoetin, which are produced in Chinese hamster ovary cell lines, epoetin delta is synthesized in human cells. Several erythropoietin preparations and darbepoetin alfa are available outside the United States, with specific agents and brand names varying by locale. "Biosimilar" erythropoietic agents (also termed "follow-on biologicals")[96–98] have been approved for use in the European Union and elsewhere. These agents are similar to already approved biological medicines such as recombinant human erythropoietin. Because it is difficult to directly compare two versions of a biopharmaceutical agent and prove equivalent efficacy and safety, these products are approved as being similar, but not necessarily identical, to the original product.

Recombinant human erythropoietin has an identical amino acid backbone as the native hormone and has biochemical and immunological properties that are virtually indistinguishable from human erythropoietin.[99,100] Darbepoetin alfa is a hyperglycosylated structural analog of recombinant human erythropoietin with a five amino acid substitution and five N-linked carbohydrate chains, two more than erythropoietin, which increases the potential maximum number of sialic acid residues from 14 to 22, increases its in vivo potency, and extends its serum half-life approximately twofold to threefold.[101,102] Methoxy polyethylene glycol-epoetin beta is a chemically synthesized substitute analog of erythropoietin with receptor binding kinetics that are different from other ESAs, and it has a very low plasma clearance. The biological half-life is approximately 6 times greater than darbepoetin and 20 times greater than erythropoietin alpha.[86,87,103–105]

All ESAs can be given to patients with CKD who are not on dialysis and to patients who are on dialysis, and can be administered intravenously and subcutaneously. Although the clinical efficacy of darbepoetin and methoxy polyethylene glycolepoetin beta appear too similar regardless of whether they are administered intravenously or subcutaneously, most studies have found that the shorter acting epoetins are more effective by approximately 50% when administered subcutaneously, so this route of administration is more cost-effective.[106–109] Intravenous administration of ESAs is recommended in the approved prescribing information in the United States for patients on hemodialysis based primarily on potential risks for antierythropoietin antibody-mediated pure red cell aplasia (PRCA) (discussed hereafter) and may be more convenient than subcutaneous administration. However, subcutaneous administration is also appropriate in hemodialysis patients and is preferred for those patients with CKD who are not on dialysis or who are on home hemodialysis or peritoneal dialysis.[1,110]

Subcutaneous administration of one particular formulation of erythropoietin alpha has been associated with antierythropoietin antibody-mediated PRCA.[111–114] Although the precise pathogenesis is not entirely known for certain, the occurrence of this disorder coincided with removal of human serum albumin from this preparation and use of polysorbate 80 instead as a stabilizing agent. The polysorbate 80 may have directly altered this product's immunogenicity or may have done so indirectly by interacting with substances leached from rubber stoppers of prefilled syringes. Errors in storage of the drug may also have been involved.[112,115–117] Fortunately, this form of PRCA appears to have nearly disappeared.[113,118]

Recommendations vary regarding the initial ESA dosing regimen and the specific Hgb level at which initiation of ESA therapy should be considered. Depending on individual circumstances, an Hgb level less than 10 to 11 g/dl is often considered an appropriate level to start an ESA, provided iron deficiency and other causes of anemia have been excluded or treated.[1,119] Once started, usage should be tailored to individual clinical circumstances, patient comorbidities, pretreatment Hgb levels, and quality of life expectations. In addition, after initiation of ESA therapy, care should be taken to titrate dosing to maintain Hgb levels in the desired range, generally in the range of 10 to 12 g/dl, to avoid targeting and maintaining Hgb levels above 13 g/dl (discussed later), and to ensure adequate provision of iron necessary for adequate erythropoiesis. There is currently a "black box warning" on the approved ESA prescribing information in the United States stating that patients with renal failure "experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dl; 14 vs. 10 g/dl) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dl." The short-acting epoetins are typically administered three times per week to hemodialysis patients. Although their pharmacokinetics would not necessarily predict that they would be effective with long dosing intervals, the epoetins can be administered as higher dose single subcutaneous doses once or twice per month with a high degree of efficacy in patients with CKD who are not on dialysis.[120–124] Darbepoetin and methoxy polyethylene glycolepoetin beta, with their longer biologic half-lives, can often be effectively administered once or twice per month in dialysis and nondialysis CKD patients.[120,125–128] A comparison of dosing recommendations from the current FDA-approved prescribing information and recent KDOQI guidelines and clinical practice recommendations[1,119] is shown in Table 7-1.

TABLE 7-1 Comparison of FDA-Approved Prescribing Information and K/DOQI Guidelines and Recommendations for ESA Use in Adults[1,119]

	APPROVED PRESCRIBING INFORMATION	K/DOQI RECOMMENDATIONS
Indications for starting ESA therapy	Nondialysis patients with symptomatic anemia should have an Hgb less than 10 g/dl. No specific recommendation for dialysis patients.	**The Hgb level at which ESA therapy is initiated should be individualized, with consideration of potential benefits and harms.**
Starting ESA dose	Epoetin: 50-100 units/kg three times weekly Darbepoetin: 0.45 mcg/kg once weekly or 0.75 mcg/kg subcutaneously once every 2 weeks (in patients not on dialysis)	Should be determined by the patient's Hgb level, target Hgb level, and clinical circumstances
Route of administration	Intravenous or subcutaneous; intravenous recommended in hemodialysis patients	Should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used. Convenience favors subcutaneous administration in CKD patients not on hemodialysis and intravenous administration in hemodialysis patients.
Hgb target range	10 to 12 g/dl	**The Hgb target should generally be in the range of 11 to 12 g/dl and should not be greater than 13 g/dl.**
Dose adjustments	Increase dose by 25% if Hgb is less than 10 g/dl and has not increased by 1 g/dl after 4 weeks of therapy or if Hgb decreases below 10 g/dl. Reduce dose by 25% if Hgb approaches 12 g/dl or if Hgb increases by more than 1 g/dl in any 2-week period. If the Hgb continues to increase, dose should be temporarily withheld until the Hgb begins to decrease, then ESA should reinitiated at a dose approximately 25% below the previous dose.	Dose adjustments should be determined by the Hgb level, target Hgb level, observed rate of increase in Hgb level, and clinical circumstances. Doses should be decreased, but not necessarily withheld, when a downward adjustment of Hgb level is needed.
Dosing in ESA-hyporesponsive patients	For patients whose Hgb does not attain a level of 10 to 12 g/dl despite appropriate dose titrations over a 12-week period, do not administer higher doses; use the lowest dose that will maintain a Hgb level sufficient to avoid the need for recurrent red blod cell transfusions. Discontinue ESA if patient needs recurrent red blood cell transfusion.	No specific recommendation.

Besides induction of iron deficiency due to stimulation of erythropoiesis and the rare, and now largely eliminated PRCA,[113] the primary adverse effects of ESAs are exacerbation of hypertension and hemodialysis access thrombosis.[1,78,110]

Iron

Adequate iron stores are essential both for innate erythropoiesis and for response to ESA therapy. Measurement of bone marrow reticuloendothelial iron is the gold standard for assessing iron stores. However, given the invasive nature of bone marrow sampling, serum tests are frequently used as surrogates, although their positive and negative predictive value for assessing iron status accurately remains debatable. A full discussion of many new advances in the understanding of iron physiology and regulation is beyond the scope of this chapter but has been well reviewed elsewhere.[129–132]

Inadequacy of iron stores can take one of two forms: absolute iron deficiency and functional iron deficiency. Absolute iron deficiency is defined by a reduction in bone marrow reticuloendothelial iron and is suggested by transferrin saturation (TSAT) less than 20% or serum ferritin level less than 100 ng/ml for predialysis patients or those on peritoneal dialysis, and less than 200 ng/ml for hemodialysis patients, although these tests are of rather low sensitivity and specificity.[133] The higher cutoff value typically recommended for hemodialysis patients relates to difficulties in mobilizing iron stores in the setting of low-grade chronic inflammation that appears to be prevalent in this population. In general, TSAT is a more sensitive marker for absolute iron deficiency, and both tests have moderate specificity (60% to 75% range).[134] Absolute iron deficiency is common among hemodialysis patients, in particular, due to loss of iron via the dialytic circuit, access surgery, and frequent phlebotomy,[135] but it is also common among patients with CKD who are not on dialysis. In fact, little or no bone marrow iron may be present in patients with CKD despite serum ferritin and TSAT levels that would not have predicted such severe iron deficiency.[133,136]

Functional iron deficiency is defined by normal bone marrow reticuloendothelial iron stores, but an inability to mobilize iron for erythropoiesis, usually stemming from systemic inflammation and/or malnutrition.[137–139] It is suggested when serum ferritin levels are greater than 100 ng/ml (200 mg/ml in hemodialysis patients) and TSAT is low. Although total body iron stores are not reduced in this setting, evidence nonetheless suggests that a course of iron repletion may raise Hgb levels[140] and lower ESA requirements.[141] Although some experts and clinical practice guidelines recommend against administration of additional intravenous iron to most patients with serum ferritin levels above 500 to 800 ng/ml[119] one small, short-term study found that even when patient's ferritin levels exceeded 800 ng/ml, administration of additional intravenous iron along with an increase in erythropoietin dose raised the Hgb level to a greater extent than an increase in erythropoietin dose alone and reduced overall erythropoietin requirements.[140,142] At this time, although TSAT and serum ferritin are the most commonly used tests for the diagnosis of iron deficiency, they are imperfect and supplemental iron administration for both diagnostic and therapeutic purposes is often indicated, using an increase in Hgb level or decrease in ESA requirement as the desired response.

A full evaluation of a patient's anemia, including complete blood count, reticulocyte count, tests for iron stores, and vitamin B12 and folate levels should be assessed when Hgb levels fall below normal, which is generally considered to be 13.5 g/dl for men and 12.0 g/dl for women,[119] and certainly prior to the initiation of ESA therapy. Patients with absolute iron deficiency should be screened for sources of occult blood loss (e.g., colonoscopy),[143] unless a source is evident from history and physical examination. Patients with absolute iron deficiency should receive iron supplementation, either as oral or intravenous iron and should have their Hgb levels remeasured when iron stores have normalized prior to initiation of ESA therapy. This is particularly important because intravenous iron supplementation alone will significantly increase Hgb levels in patients with iron deficiency, with many patients achieving Hgb levels of 10 to 12 g/dl without ESA treatment.[136,144,145]

Adequacy of iron stores should be reassessed approximately 1 to 2 months after initiation of ESA therapy, as treatment will often deplete iron stores. Patients demonstrating continued (or new) iron insufficiency should receive another course of repletion, and consideration should be given to maintenance iron therapy for those with continual iron insufficiency. In addition, if not already done, sources of occult blood loss should be investigated. Once Hgb has reached a steady state and a constant ESA dose reached, measurement of iron stores can be made every 3 months. Changes in Hgb, ESA dose titration, and marginal iron stores should prompt more frequent assessment thereafter.

By virtue of repeated blood loss and chronic inflammation, nearly all hemodialysis patients will require maintenance therapy to maintain adequate iron stores.[146] Despite this therapy, patients will frequently develop absolute or functional iron deficiency and require additional repletion, so iron stores should be checked regularly in this population.

A number of both oral and intravenous iron preparations are already commercially available for use. Oral formulations include ferrous gluconate, ferrous sulfate, and ferrous polysaccharide. Intravenous preparations include iron dextran, with two different preparations available in the United States, iron sucrose, sodium ferric gluconate in sucrose complex, and ferumoxytol. Choice among intravenous agents is often governed by formulary considerations in dialysis units; there is little evidence to suggest superior efficacy of any one agent over another. Use of iron dextran has waned over the past decade, at least in the United States, due to concerns of higher rates of severe reactions including anaphylaxis and death compared to other intravenous iron preparations.[147–156] Data suggest that there are safety differences between the two available iron dextran formulations, however, and it is not clear that avoidance of all iron dextrans is necessary.[149,157–160]

Either oral or intravenous iron supplementation preparations can be effective both in patients with CKD who are not on dialysis and those with CKD who are on peritoneal dialysis,[161] but intravenous therapy is more effective and often recommended in hemodialysis patients.[110,161–168] Oral iron repletion should be accomplished using a total daily dose of 200 mg of *elemental iron*. This is often given in divided doses to minimize gastrointestinal side effects such as constipation. Individual iron preparations vary in their content of elemental iron; none has been shown to be clearly superior in terms of efficacy or tolerability. One small study suggested that an oral heme iron preparation may be effective and well-tolerated[169] but has not been studied in direct comparison with other oral iron preparations.

For CKD patients not on dialysis and peritoneal dialysis patients who do not respond to a one-to-two month course of oral iron, intravenous iron repletion should be considered. Iron sucrose can be administered in two to three 200 to 300 mg doses spaced 1 week apart, so as to provide approximately 1 g of elemental iron and can often be given by a rapid intravenous push.[170,171] Sodium ferric gluconate can be administered as three to four 250 mg doses spaced 1 to 2 weeks apart so as to provide 750 to 1000 mg of elemental iron.[171] Ferumoxytol is a new iron preparation that can be administered in doses larger than iron sucrose or sodium ferric gluconate.[172–175]

In hemodialysis patients, intravenous iron is the therapy of choice.[110] Typically, repletion is accomplished via administration of sodium ferric gluconate (125 mg/treatment for eight treatments), iron dextran, or iron sucrose (100 mg/treatment for ten treatments) so as to provide 1 g of elemental iron. This iron load can be repeated as needed, and then once iron stores are adequate, maintenance therapy is recommended. This can be accomplished by a variety of regimens that typically provide for 25 to 100 mg of elemental iron on a weekly basis or lower doses at each hemodialysis treatment.[176,177]

Other Therapies

Whereas ESAs and iron repletion are the primary therapeutic modalities for anemia management in patients with CKD, other agents have been investigated for potential roles in augmenting the effect of ESA treatment, although none are of proven efficacy or clinical value, and none have been shown to enhance patient outcomes.[110,178,179] Vitamin C (ascorbic acid), administered intravenously at each hemodialysis session, has been shown in several studies to improve ESA responsiveness, particularly in hemodialysis patients with high serum ferritin levels and functional iron deficiency.[180–185] This effect is thought to be through antioxidant effects, mobilization of iron stores for erythropoiesis, and enhancement of iron use. Long-term safety has not been proven, although published studies have reported few, if any adverse effects. In hemodialysis patients with high ferritin levels and no detectable cause for ESA responsiveness, a short course of intravenous vitamin C might be reasonable if other efforts to achieve target Hgb levels are not successful.[178]

Similarly, supplemental L-carnitine in dialysis patients has been proposed as an adjuvant to ESA therapy.[186–189] L-carnitine is a carrier molecule that is involved in the transport of long-chain fatty acids into mitochondria; it is also thought to be involved in the metabolism of acyl CoA, a cellular toxin that accumulates in renal failure, to other less toxic compounds. The mechanism by which L-carnitine supplementation might improve anemia in patients with CKD is not clear. However, given limited quality of studies of L-carnitine, uncertainties regarding identification of patients who might be appropriate candidates for treatment and reimbursement issues, the clinical role of L-carnitine as an ESA adjuvant remains debatable.[110,190,191]

Prior to the advent of ESAs, androgens were sometimes used as a transfusion-sparing strategy among primarily male

dialysis patients. Proposed mechanisms of action include increased renal and nonrenal erythropoietin production, increased red cell survival, and enhanced sensitivity of erythroid precursors to erythropoietin. A few studies have suggested that treatment with androgens alone remains an acceptable alternative to the use of ESAs, particularly in men.[192–194] Other studies examined the role of adjuvant androgen therapy given in addition to ESAs in hemodialysis and peritoneal dialysis with disparate results;[195–197] given the frequent side effects of androgen therapy, their place in modern anemia management in patients with CKD is limited and is not recommended in clinical practice guidelines.[1,110,198]

Pentoxifylline[199,200] and statins,[201,202] both with putative antiinflammatory properties, have also been suggested to enhance ESA responsiveness but are of unproven clinical utility.

TARGET HEMOGLOBIN LEVELS FOR ERYTHROPOIESIS STIMULATING AGENT–TREATED PATIENTS

Ideally, the Hgb level achieved in each ESA-treated patient with CKD would be individually tailored depending on such factors as functional capacity and functional limitations, employment status, other comorbidities such as coronary artery disease and heart failure, and life expectancy. Unfortunately, target Hgb levels are generally influenced more by regulation by the FDA and healthcare payers, quality assurance programs in dialysis units, and clinical practice guideline recommendations. Most observational and prospective studies have demonstrated that better outcomes in terms of quality of life, hospitalization rate, and mortality in patients with CKD are associated with Hgb levels in the range of approximately 11 to 13 g/dl.[42,43,72,76,203,204] There is also increasing evidence that there is little benefit and even potential risk to targeting or maintaining Hgb levels of 13 g/dl or higher in many patients with CKD.[40,45,65,66,78,79,119]

There are now at least four large prospective studies, and several other smaller ones, evaluating the effect of targeting normal or near-normal Hgb levels in patients with CKD. The Normal Hematocrit Trial in hemodialysis patients with cardiac disease was terminated early when it was determined that the group targeted to normal values had a higher mortality that was approaching, but had not yet attained, statistical significance. Mortality rates were 7% higher in the normal Hct group than in the low Hct group. There was also a higher incidence of vascular access thrombosis in the higher Hct group.[66,67]

The CHOIR trial randomly assigned patients with CKD and anemia to achieve a target Hgb of either 13.5 or 11.3 g/dl, with the primary study endpoint being a composite of death, myocardial infarction, stroke, and hospitalization for heart failure without renal replacement therapy.[45] The study was stopped early when it was determined that is was unlikely to show any benefit of the higher Hgb level and there was a significantly higher number of events in the high Hgb group. There was no improvement in quality of life with higher Hgb levels. In the CREATE trial, patients with CKD and anemia were randomly assigned to a normal (13 to 15 g/dl) or subnormal (10.5 to 11.5 g/dl) Hgb level.[40] The primary endpoint was a composite of eight cardiovascular events, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, hospitalization for angina pectoris or arrhythmia, or complications of peripheral vascular disease. At 3 years, there was a similar risk of experiencing the primary endpoint in both groups, although there was a nonsignificant trend toward more events in the high Hgb group. Quality of life measures improved in the high Hgb group. Other smaller prospective studies have also been unable to demonstrate significant benefit of targeting or maintaining target Hgb levels above 13 g/dl.[65]

In treat (Trial of Darbepoetin Alfa in type 2 Diabetes and Chronic Kidney Disease) patients with CKD and diabetes were randomly assigned to receive darbepoetin to achieve a Hgb level of approximately 13 g/dl or placebo with darbepoetin results when the Hgb was < 9.0 g/dl.[46a] The primary end points were the composite of death or a cardiovascular event and of death or end-stage renal disease. At 48 months, there was not a significant difference between group for either composite endpoint but there was a significant increase in the risk of fatal or non fatal stroke in the darbepoetin group.

United States Regulatory and Fiscal Policy

The use of ESAs in dialysis patients in the United States has been governed by various regulatory policies since recombinant human erythropoietin was approved by the FDA in 1989, including policies governing reimbursement for ESAs to dialysis and other healthcare providers. The target Hct range for epoetin therapy approved by the FDA when the drug was initially introduced was 30% to 33%. Currently, a boxed warning on ESAs advises physicians to adjust ESA doses to maintain the lowest Hgb level necessary to avoid the need for blood transfusions and to "individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dl."[205]

Clinical Practice Guidelines for Erythropoiesis Stimulating Agent and Therapy

Several national and international organizations and societies have developed clinical practice guidelines and recommendations for anemia management in patients with CKD, including specific target Hgb and iron levels;[1,110,119,179,206–209] these are generally similar although differences in some of the specifics, such as upper and lower Hgb level limits, do exist.[210] All have concluded that partial correction of anemia to an Hgb level of at least 10 to 11 g/dl in patients with ESRD and CKD improves physiological and clinical parameters and quality of life compared to lower Hgb levels.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) last published its full guidelines in 2006[211] and updated them in 2007.[119]

In the 2006 guidelines, K/DOQI recommended that the Hgb level be maintained at 11 g/dl or higher and also stated that there was insufficient evidence to routinely recommend maintaining Hgb levels at or above 13 g/dl in ESA-treated patients. In 2007, largely in response to new studies discussed earlier indicating potential harm and an absence of clear evidence for benefit from higher Hgb levels, an update was published indicating that the **selected Hgb target should generally be in the range of 11 to 12 g/dl** and that in **dialysis and nondialysis patients with CKD, the Hgb target should not be greater than 13 g/dl.**[119]

The new guidelines also suggested that **selection of the specific Hgb target and the Hgb level at which ESA therapy is initiated should include consideration of potential benefits (such as quality of life and avoidance of transfusion) and potential harms individually for each patient.** It is important to note that these targets apply only to patients treated with ESAs, and they should not preclude administration of iron or suggest the need for phlebotomy in patients with naturally-occurring higher Hgb levels.

The most recent K/DOQI recommendations suggest maintaining TSAT above 20% in all patients, serum ferritin levels above 200 ng/ml in hemodialysis patients, and serum ferritin levels above 100 ng/ml for CKD and peritoneal dialysis patients. In contrast to earlier recommendations, the 2006 guidelines do not specify an upper limit for TSAT (earlier guidelines recommended against levels above 50%). The newer guidelines also indicate that there is insufficient evidence to recommend routine administration of additional intravenous iron to patients with serum ferritin levels above 500 ng/ml but that individualized decisions regarding iron therapy in such patients should consider ESA responsiveness, TSAT and Hgb level, and the patient's clinical status.[1] There continues to be a debate about the need to limit additional iron in patients with high serum ferritin levels, particularly when TSAT levels are not elevated.[140,212–215]

European Best Practice Guidelines (EBPG) published in 2004 not only recommended that ESA therapy be used to maintain Hgb levels at or above 11 g/dl in all patients with CKD, but also recommended that Hgb levels of 12 g/dl or higher be avoided for those with cardiovascular disease or diabetes, and that levels above 14 g/dl should generally be avoided.[206] An update of these guidelines stated that although maintaining Hgb levels of 11 g/dl or greater "appears reasonable. . .the actual evidence for choosing this value is also very limited."[216] In addition, these guidelines recommended that Hgb "values of 11–12 g/dl should be generally sought in the CKD population without intentionally exceeding 13 g/dl." In 2004, the EBPG recommended lower limits of ferritin and TSAT of 100 ng/ml and 20%, respectively, with target ranges of 200 to 500 ng/ml and 30% to 50%, respectively,[206] but those guidelines now agree with the updated K/DOQI guidelines.[216]

Erythropoiesis Stimulating Agent Hyporesponsiveness

Not all patients have a brisk or fully desired therapeutic response to standard ESA doses. Often, this is because of hyporesponsiveness or resistance to ESA therapy. These states are most relevant to (and most well-studied in) hemodialysis patients, and definitions pertain specifically to this population. However, the underlying principles and causes do apply to certain CKD and peritoneal dialysis patients and should be considered in these populations when appropriate. Hyporesponsiveness to ESA therapy is clearly associated with poorer outcome than is responsiveness to lower ESA doses.[217]

Although there are no widely accepted and scientifically validated definitions, a reasonable definition of ESA hyporesponsiveness is an epoetin requirement of more than 150 to 300 unit/kg intravenously three times per week (or equivalent) to achieve target Hgb levels. ESA resistance may be defined as the inability to achieve target Hgb levels despite ESA doses in this range.[81,137,218] Whereas ESA hyporesponsiveness is common, resistance is rare, and it occurs in less than 3% of hemodialysis patients.[81]

The most common cause of ESA hyporesponsiveness is iron deficiency.[137,219] Provided that adequate monitoring and repletion of iron stores is undertaken, this cause should be apparent, yet evidence suggests that nearly 25% of dialysis patients treated with ESAs are iron deficient.[220,221] These observations underscore the need for vigilance with respect to iron monitoring and management among patients with CKD and anemia.

Among iron replete patients, inflammation and infection are important causes of ESA hyporesponsiveness.[222] Mechanistically, this effect is believed to derive from disruption of erythropoiesis in the bone marrow by proinflammatory cytokines such as interleukin-1, tumor necrosis factor-α, and interferon-γ.[17,222] Subclinical inflammation, as might be suggested by elevated C-reactive protein levels or other markers of malnutrition and inflammation, are also associated with ESA hyporesponsiveness.[17,223–225] Even periodontitis may be a cause of reversible ESA hyporesponsiveness.[226] In cases where systemic inflammation is suspected as a cause of ESA hyporesponsiveness, but no source is identified, consideration should be given to the possibility of occult infection of thrombosed arteriovenous access grafts.[227]

Hospitalized patients have lesser degrees of ESA responsiveness than their nonhospitalized counterparts.[228] Likely, this relates to the higher prevalence of inflammation, infection, and malnutrition—and frequent phlebotomy—in this population. Other potential contributors to ESA hyporesponsiveness include inadequate dialytic clearance, secondary hyperparathyroidism, aluminum overload, and deficiency in vitamin B_{12} and folic acid.[137,218] Administration of ACE inhibitors and ARBs has also been suggested to inhibit the response to ESAs. The underlying mechanisms may relate to reduction in erythroid burst forming units in the bone marrow due to decreased angiotensin-II synthesis or decreased degradation of an inhibitor of erythropoiesis by ACE inhibitors or by direct inhibition of the erythropoietic stimulating effect of angiotensin-II by ARBs.[29,30,229–233] Although the clinical impact of this effect is small in most patients, adjustment of renin-angiotensin system inhibition can be considered as an approach that may improve Hgb levels or responsiveness to ESAs. Whether the magnitude of the inhibition of erythropoiesis by ACE inhibitors compared to ARBs is significantly different is not known.

It has long been established that severe secondary hyperparathyroidism is associated with impaired erythropoiesis, presumably due to disruption of the bone marrow architecture although toxic effects of parathyroid hormone on erythropoietin synthesis, erythropoiesis, and red blood cell survival have also been postulated.[234–236] In previous years when aluminum-containing phosphate binders were more commonly used in dialysis patients, accumulation of aluminum was also associated with anemia, typically with a microcytosis indicative of an inhibitory effect of aluminum on iron use during erythropoiesis.[237–240]

Among predialysis CKD patients, older age, higher body mass index, and diabetes as causes of kidney disease are

associated with ESA hyporesponsiveness.[241] Unfortunately, age is not a modifiable risk factor, and evidence is lacking as to whether clinically obtainable weight reduction and diabetic control improve ESA sensitivity.

When reversible causes for ESA hyporesponsiveness are detected, appropriate therapies should be instituted. Among patients for whom no etiology is identified, the clinician must consider the possibility of PRCA on the basis of antibody formation against erythropoietin, particularly in the cases of patients receiving subcutaneous ESA therapy.[242,243]

EMERGING AND CONTROVERSIAL ISSUES

Erythropoiesis Stimulating Agent Toxicity

In large observational studies, hemodialysis patients with lower Hgb levels (less than 11 to 12 g/dl) had higher hospitalization rates and worse survival rates than those with higher Hgb levels.[42,76,203] As discussed previously, in several large prospective, randomized controlled trials, however, hemodialysis patients and patients with CKD not on dialysis targeted to achieve normal or near-normal Hgb levels tended to have poorer outcomes for various composite outcomes and worse survival.[40,45,65,66] In at least two of these studies, though, adverse outcome appeared to be less associated with achieving a higher Hgb level but more associated with failure to achieve the specific Hgb target.[66,244] In observational studies, hemodialysis patients with lower achieved Hgb tended to be treated with higher ESAs doses (i.e., have greater ESA hyporesponsiveness); a secondary analysis of one of the recent large trials in patients with CKD also found that high ESA doses (and failure to achieve target Hgb level) rather than target or achieved Hgb level appeared to independently explain the poorer outcome in patients assigned to the higher Hgb target group.[244] Others have also found that requiring or receiving higher ESA doses was independently associated with higher mortality.[73] This commonality—that in both cases patients receiving higher doses of ESAs tended to have poorer outcomes—has led some to speculate that particularly high doses of ESAs may have adverse effects on survival that are not mediated by changes in Hgb concentration.[74,244–248]

Whether there is direct clinical toxic effect of high doses of ESAs remains uncertain.[249] This apparent effect may be due to other confounding clinical factors, but it may also be due to direct effects of ESAs, such as increasing blood pressure and blood viscosity, promoting inflammation, and inhibiting antifibrinolysis.[250,251] In addition, it has been suggested that ESA therapy may promote thrombocytosis, and thereby thrombosis, by depleting iron stores.[252–254] Formal recommendations about avoidance of high-dose ESA therapy have not been made, although careful scrutiny for underlying causes of ESA-hyporesponsiveness in patients receiving particularly high doses would be advisable.

Hemoglobin Cycling

The current paradigm of anemia management, in particular efforts to maintain Hgb levels within a narrow range (i.e., 11 to 12 g/dl) with oftentimes frequent changes in ESA and iron doses, tends to cause substantial variability in Hgb levels over time, particularly among hemodialysis patients.[72,255–258] Given the implied fluctuations in tissue oxygen delivery and the need for on again–off again activation of cardiac compensatory changes, it is possible that these fluctuations are detrimental to survival. Some studies have demonstrated an association between Hgb cycling and increased morbidity and mortality,[258–260] whereas others have not.[261,262] Underlying changes in ESA and iron doses and other associated clinical conditions rather than fluctuations in Hgb level may explain any association of Hgb variability and outcomes. Whether intravenous ESA administration compared to subcutaneous ESA administration and whether longer-acting ESAs or the use of extended dosing intervals with epoetin reduces short-term Hgb variability is not known for certain and may require further study if clinical implications of Hgb variability are confirmed.[263–265]

Transfusion Avoidance

One of the specific aims of ESA therapy is to reduce transfusion of red blood cells. The ability to reduce transfusions was shown dramatically in early clinical trials of erythropoietin in hemodialysis patients with severe anemia[13,81] and to a lesser extent with higher Hgb levels.[66,67] Analysis of trends in transfusion rates from 1992 in hemodialysis patients showed a decrease of more than twofold with most of the decrease occurring in the first 5 years after erythropoietin became available for clinical use.[266] In a secondary analysis of a previously published study in hemodialysis patients randomized to Hgb targets of 9.5 to 11.5 g/dl or 13.5 to 14.5 g/dl, annualized transfusion rates were approximately 40% lower in high-target subjects.[267] In TREAT ([46a]), darbepoetin treatment reduced transform by > 40%. It is also not clear what level of Hgb in CKD or dialysis patients is the most appropriate indication for transfusion.

Iron and Infection

Iron sequestration is one means by which the body protects itself against invading pathogens. Thus, some have speculated that administration of intravenous iron may promote infection. Studies have demonstrated an association between increased rates of bacterial infection and colonization and intravenous iron administration in hemodialysis patients.[268,269] In addition, baseline ferritin levels have been shown to predict development of bacteremia over the following year.[270,271] However, others have noted that ferritin is an acute phase protein, thus suggesting the possibility that the observed associations were confounded and that there is not a direct relationship between iron administration and bacterial infection in hemodialysis patients.[177,272–274] Nonetheless, many clinicians postpone supplemental iron administration during bouts of acute infection. Additional studies are needed to clarify the potential association between iron stores and infectious outcomes.

A full list of references are available at www.expertconsult.com.

Chapter 8

CHRONIC KIDNEY DISEASE-MINERAL BONE DISORDER

Sharon M. Moe, M.D.

In people with healthy kidneys, normal serum levels of phosphorus and calcium are maintained through the interaction of three hormones: parathyroid hormone (PTH), 1,25$(OH)_2$D (calcitriol), the active metabolite of vitamin D, and phosphatonins, of which fibroblast growth factor 23 (FGF-23) is best described. These hormones act on three primary target organs: bone, kidney, and intestine. The kidneys play a critical role in the regulation of normal serum calcium and phosphorus concentrations, convert vitamin D into calcitriol, and respond to PTH and FGF-23. Thus, derangements are common in patients with chronic kidney disease (CKD). Abnormalities are initially observed in patients with GFR levels around 45 to 50 ml/min/1.73 m^2 and are uniformly found at GFR levels less than 30 ml/min/1.73 m^2. With the progressive development of CKD, the body attempts to maintain normal serum concentrations of calcium and phosphorus; at some point in the progression of CKD, this normal homeostatic response becomes maladaptive. In the end, the progression of kidney disease is eventually associated with: 1) altered serum levels of calcium, phosphorus, parathyroid hormone, and vitamin D; 2) disturbances in bone modeling or remodeling with the development of fractures or impaired linear growth in children; and 3) extraskeletal calcification in soft tissues and arteries. Collectively, these abnormalities are called Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) (Table 8-1).[1] In this chapter, the physiology and clinical consequences of these three components will be discussed, followed by treatment recommendations.

BIOCHEMICAL ABNORMALITIES OF CHRONIC KIDNEY DISEASE-MBD

Phosphorus

Normal Phosphorus Physiology

Phosphorus is critical for numerous physiological functions, including skeletal development, mineral metabolism, cell membrane phospholipid content and function, cell signaling, platelet aggregation, and energy transfer through mitochondrial metabolism. Because of its importance, normal homeostasis maintains serum phosphorous concentrations between 2.5 to 4.5 mg/dl (0.81 to 1.45 mmol/L). Levels are highest in infants and decrease throughout growth, reaching adult levels in the late teens. Total adult body stores of phosphorus are approximately 700 g, of which 85% is contained in bone in the form of hydroxyapatite. Of the remainder, 14% is intracellular, and only 1% is extracellular. Of this extracellular phosphorus, 70% is organic (phosphate) and contained within phospholipids, and 30% is inorganic. The inorganic fraction is 15% protein bound, and the remaining 85% is either complexed with cations or circulates as the free monohydrogen or dihydrogen forms. Thus, serum measurements only reflect a minor fraction of total body phosphorus; and therefore do not accurately reflect total body stores in the setting of the abnormal homeostasis that occurs in CKD. The terms phosphorus and phosphate are often used

TABLE 8-1 Kidney Disease Improving Global Outcomes (KDIGO) Classification of CKD-MBD and Renal Osteodystrophy

Definition of CKD-MBD
A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: • Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism • Abnormalities in bone turnover, mineralization, volume, linear growth, or strength • Vascular or other soft tissue calcification
Definition of Renal Osteodystrophy
• An alteration of bone morphology in patients with CKD • One measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

(From S. Moe, T. Drueke, J. Cunningham, et al., Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO), Kidney Int. 69 [2006] 1945-1953.)

interchangeably, but the term phosphorus means the sum of the two physiologically occurring inorganic ions in serum, hydrogen phosphate (HPO_4^{2-}), and dihydrogen phosphate ($H_2PO_4^-$).

Phosphorus is contained in almost all foods. The average American diet contains approximately 1000 to 1400 mg phosphate per day, and the recommended daily allowance is 800 mg/day. Approximately two thirds of the ingested phosphorus is excreted in the urine, and the remaining one third in stool. Unfortunately, foods high in phosphate are generally also high in protein, making it challenging to balance dietary phosphorus restriction against the need for adequate protein intake in patients with CKD. Indeed, most well-nourished dialysis patients are in positive phosphorus balance. Roughly 60% to 70% of consumed phosphorus is absorbed, so about 4000 to 5000 mg of phosphate per week enters the extracellular fluid. Phosphate is often added to processed foods, and the amount of phosphate from these sources is significant but difficult to quantify. However, educational programs that teach patients to read labels and be aware of additives can lead to lowered serum phosphorus levels.[2] However, dietary phosphate restriction alone, although an important component of effective phosphorus management, is usually not sufficient to control serum phosphate levels in most dialysis patients.

Between 60% and 70% of dietary phosphate is absorbed by the gastrointestinal tract, in all intestinal segments. Phosphorus absorption is dependent on both passive transport related to the concentration in the intestinal lumen and active transport stimulated by calcitriol, the active metabolite of vitamin D. The passive absorption is dependent on luminal phosphorus concentration and occurs via the epithelial brush border sodium-phosphorus cotransporter (Npt2b) that sits in a "ready to use" vesicle in response to acute and chronic changes in phosphorus concentration.[3] Medications or foods that bind intestinal phosphorus (antacids, phosphate binders, and calcium) can decrease the net amount of phosphorus absorbed by decreasing the free phosphate for absorption. Calcitriol can upregulate the sodium-phosphate cotransporter and therefore actively increase phosphate absorption; however, there is near normal intestinal absorption of phosphorus in the absence of vitamin D.

Most inorganic phosphate is freely filtered by the glomerulus. Approximately 70% to 80% of the filtered load is reabsorbed in the proximal tubule, which serves as the primary regulated site of the kidney. The remaining 20% to 30% is reabsorbed in the distal tubule. Factors that increase phosphorus excretion are primarily increased plasma phosphate concentration, PTH, and FGF-23. Conversely, acute or chronic phosphorus depletion will decrease excretion. Renal phosphorus excretion is also increased, although to a lesser extent, by volume expansion, metabolic acidosis, glucocorticoids, calcitonin, growth hormone, and thyroid hormone. The majority of this regulation occurs in the proximal tubule via Npt2b.[3] Similar to the intestine, Npt2b can be acutely moved to the brush border in the presence of acute or chronic phosphorus depletion. Alternatively, after a phosphorus load or in the presence of PTH, the exchanger is removed from the brush border and catabolized.[4]

Renal phosphorus excretion is exquisitely sensitive to changes in the serum phosphorus level. This has led to the concept that there are hormones that regulate phosphorus excretion called phosphatonins. This concept is further supported by the observation that certain tumors can produce renal phosphorus wasting and that surgical removal of the tumors cures the wasting. Three phosphatonins have now been identified: secreted frizzled-related protein 4 (sFRP-4), matrix extracellular phosphoglycoprotein (MEPE), and FGF-23.[5] Mutations in FGF-23 have been identified in X-linked hypophosphatemic (XLH) rickets,[6] and elevated serum levels of FGF-23 have been found in both XLH and oncogenic osteomalacia.[7] FGF-23 appears to be the most relevant in the setting of CKD and thus will be discussed in more detail.

FGF-23 is predominately produced from bone cells (osteocytes and bone lining cells) during active bone remodeling, but mRNA is also found in heart, liver, thyroid/parathyroid, intestine and skeletal muscle.[8] FGF-23 requires the coreceptor klotho for binding to its receptor[9,10] as inactivating klotho in FGF-23 overexpressing mice reverses biochemical and skeletal abnormalities.[11] Klotho is found in the distal tubule and is down regulated in aging and CKD.[10] Once active, FGF-23 regulates Npt2a independently of PTH and affects the conversion of 25(OH)D to $1,25(OH)_2D$ by inhibition of the 1α-hydroxylase enzyme in the renal tubules,[12] leading to hypophosphatemia and inappropriately normal or low calcitriol levels. FGF-23 also stimulates PTH.[13] Mice with targeted ablation of FGF-23 confirm these physiological effects of FGF-23: hyperphosphatemia, inappropriately low PTH, increased calcitriol, and bone loss.[14] Overexpression of FGF-23 in mice leads to the progressive development of secondary hyperparathyroidism.[15] FGF-23 gene expression in bone is regulated by both phosphorus and calcitriol, even in uremic animals.[16]

To summarize, (Figure 8-1) the normal homeostatic response to increased phosphorus levels (or a chronic phosphorus load) is increased PTH and FGF-23, the latter from bone. Both the elevated PTH and FGF-23 increase urinary phosphorus excretion. The two hormones differ in respect to their effects on the vitamin D axis. PTH stimulates 1α-hydroxylase activity, thereby increasing the production of $1,25(OH)_2D$, which in turn negatively feeds back on the parathyroid gland to decrease PTH secretion. In contrast, FGF-23 inhibits 1α-hydroxylase activity, thereby decreasing

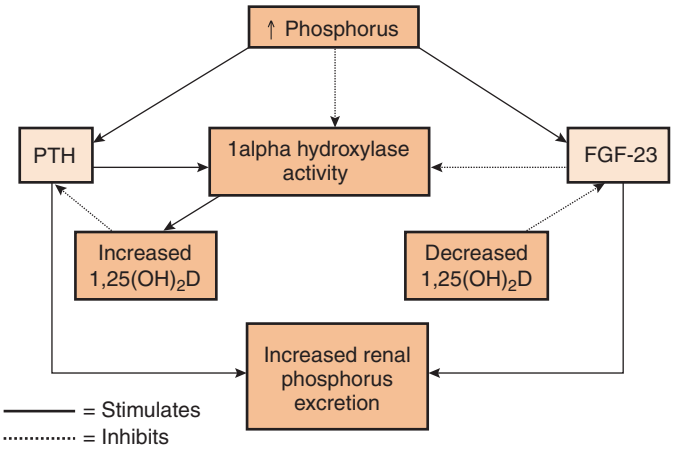


FIGURE 8-1 Regulation of serum phosphorus levels. As phosphorus levels increase (or there is a chronic phosphorus load), both PTH and FGF-23 are increased. Both the elevated PTH and FGF-23 increase urinary phosphorus excretion. The two hormones differ in respect to their effects on the vitamin D axis. PTH stimulates 1α-hydroxylase activity, thereby increasing the production of $1,25(OH)_2D$, which in turn negatively feeds back on the parathyroid gland to decrease PTH secretion. In contrast, FGF-23 inhibits 1α-hydroxylase activity, thereby decreasing the production of $1,25(OH)_2D$ feeding back to stimulate further secretion of FGF-23. *Solid line*, stimulates; *dashed line*, inhibits.

the production of calcitriol feeding back to stimulate further secretion of FGF-23. Because PTH is also stimulated in response to hypocalcemia, this proposed homeostatic loop implies that the effects of PTH would predominate in the setting of high phosphorus and low calcium, whereas FGF-23 would predominate in the setting of high phosphorus and normal or high calcium.[5]

Phosphorus Abnormalities in Chronic Kidney Disease

The ability of the kidneys to control phosphate becomes impaired at glomerular filtration rates of approximately 50 to 60 ml/min/1.73 m^2. Frank hyperphosphatemia is observed in most subjects once the GFR is less than 25 to 30 ml/min/1.73 m^2. Although phosphorus levels are maintained in the "normal" range in patients with CKD stages 3 and 4 (GFR 30 to 60 ml/min/1.73 m^2 and 15 to 30 ml/min/1.73 m^2, respectively), there is a gradual increase in the serum level[17,18] with progressive CKD, indicating that a new "steady state" of slightly higher serum phosphorus, and increased PTH levels. The maintenance of phosphate levels in the normal range (although perhaps rising) when the GFR is between 50 and 30 ml/min/1.73 m^2 has been thought to occur at the expense of continued increase in PTH secretion. This finding was first observed by Slatopolsky and colleagues based on a dog model with progressive kidney resection resembling progressive CKD. In animals treated with a normal phosphorus diet, fractional phosphate excretion rose, and PTH levels increased over 20-fold. However, in animals fed a low phosphate diet, there was no change in fractional phosphorus excretion and no change in the PTH levels. This rise in serum PTH at the expense of maintaining normal serum phosphorus is a major mechanism by which secondary hyperparathyroidism develops and is often referred to as the "trade off hypothesis."[19] Human studies, controlling for changes in calcium, also found that phosphorus loading increased PTH, and conversely, phosphorus restriction inhibited the rise in PTH.[20] Additional studies in isolated parathyroid glands or cells confirm a direct role of phosphorus on the regulation of PTH synthesis through multiple mechanisms.[21–24] Hyperphosphatemia also indirectly increases PTH by inhibiting the activity of 1α-hydroxylase, thereby reducing the conversion of 25(OH)D to $1,25(OH)_2D$. This reduction in $1,25(OH)_2D$ directly leads to increased PTH secretion.

Emerging data also indicate a possible role of FGF-23 on abnormal phosphorus homeostasis in CKD, as detailed earlier. As shown in Figure 8-2, there is a progressive rise of PTH and FGF-23 and decrease in calcitriol levels with loss of kidney function.[25] These elevated levels of FGF-23 would further decrease the circulating levels of $1,25(OH)_2D$, which together with hyperphosphatemia and the direct effect of FGF-23 on the parathyroid gland would exacerbate secondary hyperparathyroidism.[26] Indeed, studies in dialysis patients have demonstrated that serum FGF-23 levels predict the development of secondary hyperparathyroidism[27] and the responsiveness to $1,25(OH)_2D$.[28] A study that measured FGF-23 in patients new to dialysis found a very strong association with subsequent mortality.[29] Whether this is a direct effect of FGF-23, or that FGF-23 is a biomarker for severe CKD-MBD, remains to be determined. Future studies will continue to lend insight into the physiological and pathological manifestations of the elevated FGF-23 observed in CKD patients.

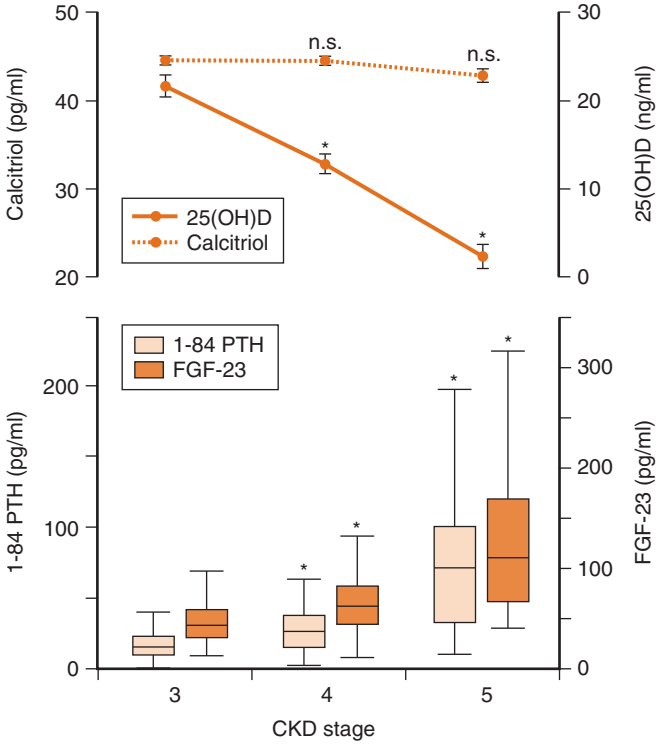


FIGURE 8-2 Hormone changes with progression of CKD. As GFR declines, there is a progressive decline in calcitriol levels, a rise in parathyroid hormone and FGF-23 levels, and persistent vitamin D deficiency. Data are presented as mean ± SEM for upper figure, and median with 25th and 75th percentiles for lower figure. (From K. Tomida, T. Hamano, S. Mikami, et al., Serum 25-hydroxyvitamin D as an independent determinant of 1–84 PTH and bone mineral density in non-diabetic predialysis CKD patients, Bone 44 [2009] 678-683.)

Calcium

Normal Calcium Physiology

Serum calcium levels are normally tightly controlled within a narrow range, usually 8.5 to 10.5 mg/dl (2.1 to 2.6 mmol/L). However, the serum calcium level is a poor reflection of overall total body calcium, as serum levels are less than 1% of total body calcium; the remainder is stored in bone. Ionized calcium, generally 40% of total serum calcium levels, is physiologically active whereas the nonionized calcium is bound to albumin or anions such as citrate, bicarbonate, and phosphate. In the presence of hypoalbuminemia, there is an increase in the ionized calcium relative to the total calcium, thus total serum calcium may underestimate the physiologically active (ionized) serum calcium. A commonly used formula for estimating the ionized calcium from total calcium is to add 0.8 mg/dl for every 1 mg decrease in serum albumin below 4 mg/dl. Unfortunately, data in CKD patients has demonstrated that this formula offers no superiority over total calcium alone, and is less specific than ionized calcium measurements.[30] In addition, the assay used for albumin may impact the corrected calcium measurement.[31] Thus, ionized calcium should be measured if more precise assessment of serum calcium levels are needed. Calcium absorption across the intestinal epithelium occurs via a vitamin D–dependent, saturable (transcellular) TRPV5 and TRPV6 transporters (animal homologues ECaC2 and CaT1)[32] and independent, nonsaturable (paracellular) pathways. The intracellular calcium then associates with calbindin 9k to be "ferried" to the basolateral membrane where calcium is removed from the enterocytes via the calcium-ATPase. TRPV6 is the main transporter responsible for intestinal calcitriol-dependent calcium absorption, with compensation by TRPV5 when needed.[32]

In the kidney, the majority (60% to 70%) of calcium is reabsorbed passively in the proximal tubule driven by a transepithelial electrochemical gradient that is generated by sodium and water reabsorption. In the thick ascending limb, another 10% of calcium is reabsorbed via paracellular transport. Although the bulk of total renal calcium reabsorption is paracellular, the regulation of reabsorption is via transcellular pathways that occur in the distal convoluted tubule, the connecting tubule, and the initial portion of the cortical collecting duct. The calcium enters these cells via TRPV5 and TRPV6 calcium channels down electrochemical gradients, binds with calbindin 28k and is transported to the basolateral membrane where calcium is actively reabsorbed by the Na^{2+}/Ca^{2+} exchanger (NCX1) and/or the Ca^{2+}-ATPase (PMCA1b).[32] Both TRPV5 and TRPV6 are localized to these distal nephron segments, with upregulation by calcium, PTH, vitamin D, and estrogen. TRPV5 is the most critical, with compensation by TRPV6, which is the opposite from compensation in the intestine.[32]

Physiological studies in animals and humans in the 1980s demonstrated the rapid release of PTH in response to small reductions in serum ionized calcium, lending support to the existence of a calcium sensor in the parathyroid glands. This calcium sensing receptor (CaR) was cloned in 1993, which led to a revolutionary understanding of the mechanisms by which cells adjust to changes in extracellular calcium. The CaR was shown to belong to the super family of G-protein coupled receptors. Activation of the CaR stimulates phospholipase C, leading to increased inositol 1,4,5-triphosphate (IP3), which mobilizes intracellular calcium and decreases PTH secretion. In contrast, inactivation reduces intracellular calcium and increases PTH secretion.[33] The CaR is expressed in organs controlling calcium homeostasis such as parathyroid gland, thyroid C cells, intestine, kidney,[33] and likely bone.[34] In the kidney, the CaR is expressed in mesangial cells and throughout the tubules. The CaR is found not only on the apical membrane of the proximal tubule and the inner medullary collecting duct, but also on the basolateral membrane of the medullary and cortical thick ascending limb and distal convoluted tubule. Activation of CaR on the thick ascending limb leads to increased intracellular free Ca^{+2}, which decreases paracellular calcium reabsorption.[35] This CaR also responds to increases in intraluminal calcium concentration by reducing antidiuretic hormone stimulated water absorption.[36] In theory, this may provide a mechanism by which the urine can stay dilute in the face of hypercalcemia and hypercalciuria to avoid dangerous calcium precipitation, and it may explain the polyuria observed in patients with hypercalciuria. The expression of the CaR is regulated by calcitriol in parathyroid, thyroid, and kidney cells, but the renal effects of CaR are both dependent and independent of PTH. In uremic animals, the expression of CaR in the parathyroid gland is down regulated by high phosphorus diet and occurs after the onset of parathyroid hyperplasia. Once down regulated, the expression can be rescued by a low phosphorus diet.[24]

Calcium Abnormalities in Chronic Kidney Disease

Similar to phosphorus, serum calcium levels are generally maintained in the normal range, at the expense of hyperparathyroidism, throughout the course of CKD until the GFR is less than 30 ml/min/1.73 m^2.[37] Late in the course of CKD, calcitriol levels are inadequate to increase intestinal calcium absorption.[38] In addition, most patients with CKD stages 3 and 4 have very low levels or urinary calcium excretion,[39] suggesting maximum tubular reabsorption. When homeostasis is normal, balance is age appropriate: children and young adults are usually in a slightly positive net calcium balance to enhance linear growth; beyond age 25 to 35, when bones stop growing, the calcium balance tends to be neutral.[40] Normal individuals have protection against calcium overload by virtue of their ability to increase renal excretion of calcium and reduce intestinal absorption of calcium by actions of PTH and calcitriol. However, in CKD the ability to maintain normal homeostasis, including a normal serum ionized calcium level, is impaired, which often leads to an inappropriate calcium balance. In CKD, the bone appears less able to take up calcium, at least in low turnover states that can be present in up to 50% of patients with CKD.[41] This has led to the concept of "calcium loading" when patients are also given a calcium-based binder because, even with normal serum levels, excess calcium intake can lead to a positive calcium balance. Without net urinary excretion or bone uptake, this may predispose the person to extraskeletal calcification.[42]

This potential for excess positive calcium balance led to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline recommendation to limit the daily ingestion of calcium in the form of calcium-containing phosphate binders to

1500 mg of elemental calcium per day. This is assuming a 500 mg intake per day from diet, for a total intake of 2000 mg per day.[43] This level is slightly below the Institute of Medicine's recommended maximum intake of calcium of 2500 mg per day for healthy adults. However, one can extrapolate the impact of this intake from several studies (reviewed in Moe and Chertow).[42] In CKD patients, approximately 18% to 20% of calcium is absorbed from the intestine. If patients are taking 2000 mg per day in total elemental calcium intake (1500 mg from binder and 500 mg from diet), and 20% is absorbed, then the net intake is 400 mg per day. On hemodialysis days, this figure is slightly greater because approximately 50 mg of calcium is infused with a 4-hour dialysis treatment using 2.5 meq/L dialysate calcium concentration. In patients on peritoneal dialysis, there is a slight efflux of calcium using a 2.5 meq/L dialysate in four daily exchanges. Thus the absorbed intake of elemental calcium from a 2000 mg elemental calcium diet (plus binders) and 2.5 meq/L calcium dialysate would be 350 to 450 mg/day. In patients taking most forms of vitamin D, net intestinal absorption would be enhanced, thereby increasing the net intake further. The excretion of calcium in stool and sweat ranges from 150 to 250 mg per day, and if patients have residual urine output, then the excretion rate may increase by 50 to 100 mg per day. Thus with 400 mg net absorbed calcium, the patients will still be in positive calcium balance (350 to 450 mg in versus 220 to 350 mg out) at the K/DOQI maximum when taking 2000 mg of total elevated calcium per day.

In an anuric patient, this positive balance of calcium load has only two "compartments" to go to: bone and extraskeletal locations. If the bone is normally remodeling, then the calcium should be deposited there; however, normal bone is not common in dialysis patients (see later). If no calcium-containing phosphate binder is taken, then the patients should be in a neutral or slightly negative balance depending on stool and sweat output. It is important to emphasize three points: First, this 1500 mg maximum intake of elemental calcium from phosphate binders in the K/DOQI guidelines is based on opinion, as there are no recent formal metabolic balance studies. Second, in patients taking vitamin D, the intestinal absorption of calcium will be increased; thus, the amount of calcium in the form of binder should probably be decreased. Third, in patients with low turnover bone disease, the bone cannot take up calcium;[41,44] thus it is more likely to deposit in extraskeletal sites, and that is the rationale for the K/DQOI recommendation that calcium containing phosphate binders not be used in patients with adynamic bone disease.[43]

Vitamin D (See Chapter 9)

Although the nephrology community often thinks of the term "vitamin D" as the active metabolite calcitriol, the correct use of the term vitamin D is for the precursor molecule.

Cholesterol is synthesized to 7-dehydrocholesterol, which in turn is metabolized in the skin to vitamin D_3. In addition, there are dietary sources of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Once in the blood, vitamin D_2 and D_3 bind with vitamin D binding protein (DBP) and are carried to the liver where they are hydroxylated by *CYP27A1* in an essentially unregulated manner to yield 25(OH)D, often called calcidiol and measured as "vitamin D." Calcidiol is then converted in the kidney to calcitriol by the action of 1α-hydroxylase (*CYP27B1*). The 1α-hydroxylase enzyme in the kidney is also the site of regulation of calcitriol synthesis by numerous other factors, including low calcium, low phosphorus, estrogen, prolactin, growth hormone, calcitriol itself,[45] and FGF-23.[46] Calcitriol mediates its cellular function via both nongenomic and genomic mechanisms. Calcitriol facilitates the uptake of calcium in intestinal and renal epithelium by increasing the activity of the voltage-dependent calcium channels TRPV5 and TRPV6, up-regulating the calcium transport protein calbindins and the basolateral calcium-ATPase.[32] It also is essential for normal bone remodeling.[47]

Early human studies demonstrated that oral calcitriol, but not the precursor hormone vitamin D_3, suppressed PTH in patients undergoing dialysis,[48] although recent experimental data demonstrated 25(OH)D also decreases PTH synthesis.[49] Intravenous calcitriol also suppressed PTH with effects observed before increases in serum calcium in dialysis patients.[50] Studies have indicated that calcidiol deficiency and insufficiency are common in CKD, as is calcitriol deficiency.[37] As will be discussed in the treatment section, these abnormalities are important in the pathogenesis of hyperparathyroidism; thus, repletion can be used to lower PTH. Vitamin D also has multiple nonbone and nonmineral effects, which are detailed in Chapter 9.

Parathyroid Hormone

Parathyroid Hormone Physiology

The primary function of PTH is to maintain calcium homeostasis by: 1) increasing bone mineral dissolution, thus releasing calcium and phosphorus; 2) increasing renal reabsorption of calcium and excretion of phosphorus; 3) increase the activity of the renal 1α-hydroxylase; and 4) enhancing the gastrointestinal absorption of both calcium and phosphorus indirectly through its effects on the synthesis of calcitriol. PTH is cleaved to an 84-amino acid protein in the parathyroid gland, where it is stored with fragments in secretory granules for release. Once released, the circulating 1-84 amino acid protein has a half-life of 2 to 4 minutes. It is then cleaved into N-terminal, C-terminal, and midregion fragments of PTH, which are metabolized in the liver and kidney. In addition, fragments are also directly released from the gland.

PTH secretion occurs in response to hypocalcemia, hyperphosphatemia, and calcitriol deficiency. The extracellular concentration of ionized calcium is the most important determinant of minute-to-minute secretion of PTH. The secretion of PTH in response to low levels of ionized calcium is a sigmoidal relationship, frequently referred to as the calcium-PTH curve. Early studies indicated that the calcium-PTH curve was shifted to the right in CKD, creating an altered set point, defined as the calcium concentration that results in 50% maximal PTH secretion. The extrapolation of this data to clinical practice was that patients with CKD required supraphysiological serum levels of calcium to suppress PTH. However, several studies failed to confirm these findings.[51] In parathyroid glands removed from

patients with severe secondary hyperparathyroidism, there was altered sensitivity to calcium (a shift to the right of the curve) when glands were incubated in the presence of phosphorus.[22] Confirming this was an in vivo study in dialysis patients demonstrating that an infusion of phosphorus shifts the calcium-PTH curve to the right.[52] Thus, it is possible that some of the earlier discrepancy in the literature regarding possible alterations of the set point in CKD may have been due to differences in serum phosphorus levels in the various studies, although methodologic differences can also explain some of this discrepancy.[51]

PTH binds to the PTH1 receptor, which is a member of the G-protein linked 7-membrane spanning receptor family. PTHrp shares homology with the first few amino acids of PTH and also binds the PTH1 receptor. In general the effects of PTH are systemic, and those of PTHrp is as an autocrine factor. In the kidney, PTHR1 is widely expressed. As detailed earlier, PTH upregulates TRPV5, TRPV6, calbindin$_{28K}$, NCX1, and PMCA1b in these distal tubule segments to facilitate calcium reabsorption.[32] PTH also facilitates phosphorus wasting by inducing the catabolism of the brush border sodium-phosphate cotransporter Npt2b.[3] In bone, PTH receptors are located on osteoblasts with a time-dependent effect. PTH administered chronically inhibits osteoblast differentiation and nodule formation, but administration of PTH in a pulse rather than a continuous manner stimulates osteoblast proliferation and mineralization.[53] PTH-induced signaling predominately affects mineral metabolism; however, there are many extraskeletal manifestations of PTH excess in CKD. These include encephalopathy, anemia, extraskeletal calcification, peripheral neuropathy, cardiac dysfunction, hyperlipidemia, and impotence.

Measurement of Parathyroid Hormone

Reliable measurements of the concentration of PTH in serum or plasma are essential for the clinical management of patients with CKD. The measurement of PTH in blood has evolved considerably (Figure 8-3).[54] In the early 1960s radioimmunoassays were developed for measurement of PTH. However, these assays proved not to be reliable owing to different characteristics of the antisera used and the realization that PTH circulates not only in the form of the intact 84-amino acid peptide but also as multiple fragments of the hormone, particularly from the middle and carboxy C-terminal regions of the PTH molecule. These PTH fragments arise from direct secretion from the parathyroid gland as well as from metabolism of PTH (1-84) by peripheral organs, especially liver and kidney. For these reasons, assays for PTH that were directed toward different parts of the PTH molecule yielded different results. Furthermore, because the kidney is the major route of elimination of the PTH fragments, values were markedly elevated in patients with advanced CKD and those requiring dialysis when compared to those determined in subjects with normal renal and parathyroid gland function.

The development of a second generation of PTH assays, the two-site immunoradiometric antibody test (commonly called "intact" assay) improved the detection of entire length of (active) PTH molecules. In this assay, a capture antibody binds within the amino terminus and a second antibody binds within the carboxy terminus. Unfortunately, this

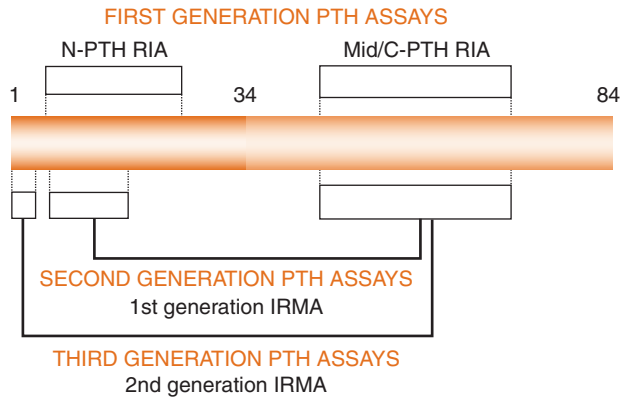


FIGURE 8-3 PTH assays. In the 1980s, only the N-terminal and mid/C-terminal PTH assays were available, both of which detected multiple PTH fragments in the circulation. First- and second-generation immunometric (IRMA) PTH assays differ with respect to the location of the epitope targeted by the labeling antibody in these assay systems. For second-generation assays, the epitope is located within the most amino-terminal portion of the molecule. Peptides missing one or more amino acid residues from the amino terminus of PTH will not be detected by second-generation immunometric PTH assays. (Adapted from W.G. Goodman, H. Juppner, I.B. Salusky, et al., Parathyroid hormone [PTH], PTH-derived peptides, and new PTH assays in renal osteodystrophy, Kidney Int. 63 [2003] 1–11.)

"intact" PTH assay also detects accumulated large C-terminal fragments, commonly referred to as "7-84" fragments, which is a mixture of multiple PTH fragments that include, and are similar in size, to 7-84 PTH.[55] In parathyroidectomized rats, the injection of a truly whole 1-84 amino acid PTH was able to induce bone resorption, whereas the 7-84 amino acid fragment was antagonistic, which explains why patients with CKD may have high levels of "intact" PTH but relative hypoparathyroidism at the bone tissue level.[56,57]

More recently, a third generation of assays have become available that truly detect only the 1-84 amino acid full length molecule or "whole" or "bioactive" PTH assays. Early reports suggested that levels of 1-84 PTH or the 1-84 PTH/large C-PTH fragment ratio may be a better predictor of bone histology in end-stage renal disease (ESRD) than standard "intact" PTH values.[58] However, other studies have not confirmed the ability of the whole PTH or the ratio to predict the diagnosis of the underlying bone disease.[59,60] A study demonstrated that although both 1-84 and non–1-84 fragments are secreted from the PTH gland in response to serum calcium levels, the secretory responses are not proportional,[61] perhaps leading to the discrepancy of these reports.

Much of the literature, and recommendations from K/DOQI bone and mineral guidelines for PTH targets,[43] was based on the second-generation Allegro assay from Nichols Diagnostic Institute, which is not currently available. These intact assay is more discriminatory than N- or C-terminal assays in patients with CKD;[62] however, its ability to discriminate between low and high bone turnover in dialysis patients as compared to bone histology is limited to very low levels (< 100 to 150 pg/ml) and very high levels (>500 pg/ml).[63,64] Furthermore, racial differences exist. In one series, the mean intact PTH level was 460 ± 110 pg/ml in African Americans with bone biopsy proven low-turnover bone disease compared to 144 ± 43 pg/ml in Caucasians with the same degree of bone turnover.[65] A study found that nearly 50% of subjects treated to maintain the intact PTH

level within the K/DOQI target range had adynamic bone disease.[66]

These data highlight that the use of tight PTH ranges as a biomarker for bone turnover is no longer valid. In addition, different available assays measure different quantities of both 7-84 and 1-84 (when added to uremic serum).[67] There are also differences in PTH results when the samples are measured in plasma, serum, or citrate, and depending on whether the samples are on ice or allowed to sit at room temperature.[68] Thus, these problems with sample collection and assay variability raise significant concerns with the validity of absolute levels of PTH, and the inability of specific values to predict underlying bone histology limits the clinical use as a bone biomarker at specific values. For these reasons, the KDIGO guidelines recommended that extremes of risk for PTH, which are less than 2 or greater than 9 times the upper limit for a given assay. Values within this range should be evaluated on trends.[69]

Clinical Consequences of Abnormal Biochemical Indices of Chronic Kidney Disease-MBD

Phosphorus

Human studies support a direct effect of elevated phosphorus on PTH secretion.[22] In vitro data support a direct effect of elevated phosphorus on vascular calcification,[70] and in humans, hyperphosphatemia is associated with increased vascular stiffening, arterial calcification, calciphylaxis, and valvular calcification.[71] Epidemiological data suggest that serum phosphorus levels above the normal range are associated with increased morbidity and mortality in patients with CKD, with the majority of studies done in dialysis patients. These studies differ in their sample size, analyses, and their chosen reference range. The inflection point or range at which phosphorus becomes significantly associated with increased all-cause mortality in dialysis patients varies between studies being 5.0 to 5.5 mg/dl (1.6 to 1.8 mmol/L),[72] greater than 5.5 mg/dl (>1.8 mmol/L),[73] 6.0 to 7.0 mg/dl (1.9 to 2.3 mmol/L)[74], and greater than 6.5 mg/dl (>2.1 mmol/L).[75–77] A DOPPS analysis demonstrates that the relationship between elevations in serum phosphorus and mortality is consistent across all countries analyzed and that if a facility had 10% more patients with phosphorus levels between 6.1 to 7.0 mg/dl and greater than 7.0 mg/dl (1.97 to 2.26 mmol/L and greater than 2.26 mmol/L), mortality risk was 5.3% and 4.3% higher, respectively.[77] Even in the nondialysis population, higher levels of serum phosphorus, even within the normal range, have been associated with increased risk of all-cause or cardiovascular mortality in patients with normal renal function who were free of cardiovascular disease,[78] in patients with coronary artery disease and normal renal function,[79] and in patients with CKD stages 3 through 5.[80] However, a subanalysis of the Modification of Diet in Renal Disease (MDRD) study failed to identify phosphorus as an independent risk factor for increased mortality in patients with CKD who were not on dialysis.[81] Thus, there is clear epidemiological data to support that patients with lower levels of phosphorus do better. Unfortunately, no study has demonstrated that lowering the serum phosphorus to a specific value leads to improved outcomes.

Calcium

In patients with CKD stages 3 through 5, there are no data to support an increased risk of mortality or fracture with increasing serum calcium concentrations. The association in stage 5D CKD patients is generally similar to that of serum phosphorus. The inflection point or range at which calcium becomes significantly associated with increased all-cause mortality varies, being greater than 9.5 mg/dl (>2.38 mmol/L),[72] greater than 10.1 mg/dl (>2.53 mmol/L),[77] greater than 10.4 mg/dl (>2.60 mmol/L),[74,76] and greater than 11.4 mg/dl (>2.85 mmol/L).[75] Globally, 50% of stage 5D CKD patients have serum calcium levels above 9.4 mg/dl (>2.35 mmol/L), and of these, 25% have serum calcium levels above 10.0 mg/dl (>2.50 mmol/L).[77] At the low end, there is little evidence of an increase in relative risk until serum levels fall below 8.4 mg/dl (>2.10 mmol/L).[77] However, in another study from the United States, the increased relative risk of mortality with low serum calcium was reversed when adjusted for covariates.[72] It is therefore unclear at what level of low serum calcium there is an increased risk. It is also important to realize that none of these studies evaluated patients receiving cinacalcet, which lowers calcium by its effects on the calcium-sensing receptor, with an expected decrease in the total serum calcium concentration. Thus, we do not know if patients with low serum calcium levels due to cinacalcet have a similar risk to those with similar serum calcium levels who are not on the drug.

Parathyroid Hormone

The target PTH in the K/DOQI guidelines for CKD stage 5D was based on the ability of PTH to predict low and high turnover bone disease.[43] Unfortunately, the assay used, the Nichols Allegro, is no longer available. More recent studies, as detailed earlier, have demonstrated that intact PTH levels within a range of 150 to 300 pg/ml are not predictive of underlying bone histology.[66] In addition, there are significant problems with assay variation. This raises concerns about the use of PTH as a biomarker of bone turnover, which has been done in clinical practice for years. However, hyperparathyroidism is a systemic disease, with multiple nonbone effects.[82] Thus, KDIGO, in establishing optimal PTH ranges, evaluated additional evidence in the form of observational data determining associations between PTH and patient level end points (mortality, cardiovascular death, fractures). The inflection point or range at which PTH becomes significantly associated with increased all-cause mortality varies between studies and ranges from above 400 pg/ml,[74] to above 480 pg/ml,[75] to above 500 pg/ml,[76] to above 511 pg/ml,[83] and to above 600 pg/ml.[72] Unfortunately, most of these analyses either do not indicate the assay type, or the data comes from PTH measured with multiple assays. Another confounding factor for these analyses is that many studies feature single-baseline PTH values or infrequent (quarterly or less) measurements. One report has suggested that the 1-84 PTH "bio-intact" or "whole" assay is a better predictor of mortality than "intact" PTH assays.[84] However, this finding needs to be confirmed. Based on these observational data, the KDIGO guidelines considered that levels of intact PTH below 2 and above 9 times the upper limit of normal for the PTH assay (<130 and >585 pg/ml for most

kits that have a upper normal limit of 65 pg/ml) represented extreme ranges of risk that should be avoided. Values within that range should be interpreted by evaluating trends, with interventions if the trends are consistently going up or down. However, it is important to recognize that there are no randomized clinical trials that demonstrate that treatment to achieve a specific PTH level results in improved outcomes.

Combinations of Biochemical Abnormalities

The relationship of biochemical parameters of CKD-MBD with outcomes is further complicated by the clinical reality that these laboratory parameters do not move in isolation from one another, but change depending on the levels of other parameters and treatments. This is best demonstrated by the work of Stevens and colleagues,[85] which assessed various biochemical combinations in concert with dialysis vintage and found that specific risks varied significantly according to three-pronged constellations. The relative risk for mortality was greatest when levels of serum calcium and phosphorus were elevated in conjunction with low levels of intact PTH and was lowest with normal levels of serum calcium and phosphorus in combination with high levels of intact PTH. In addition, duration of dialysis significantly impacted the results. A DOPPS study also evaluated combinations of serum parameters of mineral metabolism and reached slightly different conclusions.[77] For example, in the setting of an elevated serum PTH (>300 pg/ml), hypercalcemia (>10 mg/dl) was associated with increased mortality risk even with normal serum phosphorus levels. Overall, it is the combination of biochemical abnormalities that has the greatest impact on mortality (Figure 8-4). Thus, the evaluation of an individual patient requires synthesis of all of the abnormalities, and unfortunately that does not easily lend itself to simple algorithms or protocols.

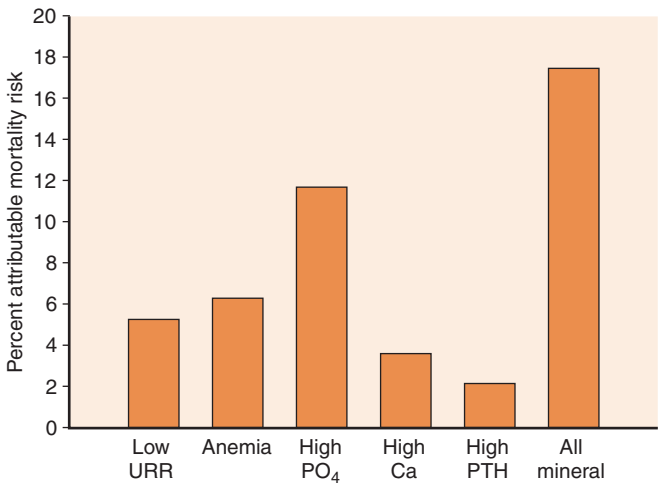


FIGURE 8-4 Mortality risk of disturbances in mineral metabolism. A study of 40,538 patients[72] identified the population attributable risk, or the percentage of risk of mortality in ESRD patients attributable to various factors, and demonstrated[72] that hyperphosphatemia conveyed the greatest risk of mortality or even more than anemia and low urea reduction ratio [URR], and that the combination of hyperphosphatemia, hypercalcemia, and elevated PTH accounted for 17.5% of the observed mortality. (From S.M. Moe, G.M. Chertow, The case against calcium-based phosphate binders, Clin. J. Am. Soc. Nephrol. 1 [2006] 697-703, using data from G.A. Block, P.S. Klassen, J.M. Lazarus, et al., Mineral metabolism, mortality, and morbidity in maintenance hemodialysis, J. Am. Soc. Nephrol. 15 [2004] 2208-2218.)

Renal Osteodystrophy

Bone Biology

The majority of the total body stores of calcium and phosphorus are located in bone. Trabecular (cancellous) bone is located predominately in the epiphyses of the long bones, and cortical (compact) bone is in the shafts of long bones and is 80% to 90% calcified. Bone consists principally (90%) of highly organized cross-linked fibers of type I collagen; the remainder consists of proteoglycans and noncollagen proteins such as osteopontin, osteocalcin, osteonectin, and alkaline phosphatase. The main bone cells are cartilage cells, which are key to bone development; osteoblasts, which are the bone forming cells; and osteoclasts, which are the bone resorbing cells. Osteoblasts are derived from progenitor mesenchymal cells located in the bone marrow. They are then induced to become osteoprogenitor cells, then endosteal or periosteal progenitor cells, and then mature osteoblasts. The control of this differentiation pathway is due to bone morphogenic proteins and the transcription factor Runx2 early and other hormones and cytokines later. Once bone formation is complete, osteoblasts may undergo apoptosis, or become quiescent cells trapped within the mineralized bone in the form of osteocytes.[86] The osteocytes are interconnected through a series of canaliculi. Although these cells were previously thought to be of little importance, it is now clear that they serve to transmit the initial signaling involved with mechanical loading.[87] Osteoclasts are derived from hematopoietic precursor cells that differentiate and are somehow "signaled" to arrive at a certain place in the bone. Once there, they fuse to form the multinucleated cells known as osteoclasts that become highly polarized, reabsorbing bone through the release of degradative enzymes. Once resorption is complete, estrogens, bisphosphonates, and cytokines can induce, and PTH can inhibit apoptosis.[86] Numerous hormones and cytokines have been evaluated, mostly in vitro, for their role in controlling osteoclast function. The control of bone remodeling is highly complex, but it appears to occur in very distinct phases: 1) osteoclast resorption, 2) reversal, 3) preosteoblast migration and differentiation, 4) osteoblast matrix (osteoid or unmineralized bone) formation, 5) mineralization, and 6) quiescent stage. At any one time, less than 15% to 20% of the bone surface is undergoing remodeling, and this process in a single bone remodeling unit can take 3 to 6 months.[86] How a certain piece of bone is chosen to undergo a remodeling cycle and how the osteoclasts and osteoblasts signal each other is due to the osteoprotegerin (OPG) and receptor activator of nuclear-factor κB system (RANK). This control system is regulated by nearly every cytokine and hormone thought important in bone remodeling, including PTH, calcitriol, estrogen, glucocorticoids, interleukins, prostaglandins, and members of the transforming growth factor–β superfamily of cytokines.[88] OPG has been successful in preventing bone resorption in animal models of osteoporosis and tumor-induced bone resorption. Not surprisingly, a new drug, denosumab, is a fully human monoclonal antibody that

inhibits receptor activator of nuclear-factor κB ligand (RANKL), and appears to be a promising therapeutic agent for osteoporosis.[89–91] Abnormalities in the OPG/RANK system have been found in renal failure[92], although the impact on bone remodeling is not yet clear.

ASSESSMENT AND CLASSIFICATION OF RENAL OSTEODYSTROPHY

Abnormalities of Bone in Chronic Kidney Disease

Disorders of mineral metabolism are also associated with abnormal bone. The gold standard test for bone quality is its ability to resist fracture under strain. In animal models, this can be directly tested with three-point bending mechanical tests. Bone quality is impaired in CKD, as there is an increased prevalence of hip fracture in dialysis patients compared to the general population in all age groups.[93–95] Dialysis patients in their 40s have a relative risk of hip fracture that is 80-fold higher than that of age- and sex-matched controls.[94] Furthermore, hip fracture in patients on dialysis is associated with a doubling of the mortality rate observed in hip fractures in patients who are not on dialysis.[95,96] In multivariate analysis, the risk factors for hip fracture include age, gender, duration of dialysis, and presence of peripheral vascular disease.[93] Other analyses found race, gender, duration of dialysis, and low or very high PTH levels as risk factors for hip fracture.[95,96] In a study of Japanese men, 21% of prevalent dialysis patients (mean age 54 ± 9 years) had vertebral fractures identified by plain radiographs, indicating that both hip and lumbar spine fractures occur independent of gender and race.[97] In the CKD population, a similar increased risk occurs.

Extremes of bone turnover found in patients with CKD significantly impact fragility and are likely additive to bone abnormalities commonly found in the aging and sedentary general population. These extremes of bone turnover that contribute to abnormal bone quality differentiate renal osteodystrophy from traditional osteoporosis, which is predominately low bone volume. The latter can be determined by bone mineral density testing (i.e., with dual energy x-ray absorptiometry, or DXA). However, DXA only evaluates how much mineral is present, not how it is arranged. In the case of renal osteodystrophy, the "arrangement" can be so aberrant as to alter quality even at high mineral content. Not surprisingly, studies have not found a relationship between DXA and underlying bone histology.[98,99] The ability of DXA to predict fractures prospectively is also not consistent in the literature. A recent metaanalysis of six studies found no increased risk of hip fracture related to bone mineral density (BMD) at the hip, but the spine and distal radius BMD values were significantly lower in patients who had a fracture than in those who did not.[100] However, no studies have shown that an intervention that changes BMD impacts fracture risk; thus, routine screening with DXA is not currently recommended in patients with advanced CKD, stages 4 and 5.

The clinical assessment of renal osteodystrophy is best done with a bone biopsy of the trabecular bone, usually at the iliac crest. The patient is given a tetracycline derivative approximately 3 weeks prior to the bone biopsy and a different tetracycline derivative 3 to 5 days prior to the biopsy. Tetracycline binds to hydroxyapatite and emits fluorescence, thereby serving as a label of the bone. A core of predominately trabecular bone is taken and embedded in a plastic material and sectioned, requiring special laboratories to process bone biopsies. The sections can then be visualized with special stains, and under fluorescent microscopy to determine the amount of bone between the two tetracycline labels, or that formed in the time interval between the two labels. This dynamic parameter assessed on bone biopsy is the basis for assessing bone turnover, which is central to discerning types of renal osteodystrophy. In addition to dynamic indices, bone biopsies can be analyzed by histomorphometry for many static parameters as well. The nomenclature for these assessments has been standardized.[101]

Traditional Classification Scheme for Renal Osteodystrophy Focused on Bone Turnover[102]

High turnover bone disease was due to secondary hyperparathyroidism, with high bone formation rates, increased cell number, and in severe cases, peritrabecular fibrosis (termed osteitis fibrosa cystic). Low turnover bone disease has low bone formation rates with either increased osteoid (unmineralized bone) called osteomalacia, or no increased osteoid but decreased cell numbers (adynamic bone disease). In the past, osteomalacia was due to aluminum deposition at the bone mineralization front that prevented appropriate mineralization. Lastly, mixed uremic osteodystrophy is a term used to identify a high turnover lesion, but with increased osteoid. Unfortunately, the latter diagnosis is not uniformly made throughout the world.

The prevalence of different forms of renal osteodystrophy has changed over the past decade. Whereas osteitis fibrosa cystica had previously been the predominant lesion, the prevalence of mixed uremic osteodystrophy and adynamic bone disease has increased. However, the overall percentage of patients with high bone formation compared to low bone formation has not changed dramatically over the last 20 to 30 years, but osteomalacia has been essentially replaced with adynamic bone disease.[103] In patients not yet on dialysis, the series of bone biopsies yield widely different results depending on the level of GFR and the country in which the study was done. However, it is clear from these data that histological abnormalities of bone begin very early in the course of chronic kidney disease. One component of bone histology that has been often overlooked is bone volume. Bone volume will be reduced when there is net resorption more than formation. This may occur with post-menopausal osteoporosis or in prolonged high turnover lesions. A study in 2006 found that bone volume was low in 46% of patients who underwent bone biopsy.[104]

At the KDIGO consensus conference in 2005 the definition of renal osteodystrophy was reexamined.[1] It was agreed that the term renal osteodystrophy should be specific to bone pathology found in patients with CKD and is one component of the mineral and bone disorders that occur as a complication of CKD-MBD. To clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, it was agreed to use three key histological descriptors—bone

turnover, mineralization, and volume (TMV system), with any combination of each of the descriptors possible in a given specimen. The TMV classification scheme provides a clinically relevant description of the underlying bone pathology as assessed by histomorphometry, which in turn helps to define the pathophysiology, and thereby guides therapy. Figure 8-5 shows how the TMV system and the traditional classification terminology intersect. Importantly, by adding the component of volume, one can see that long standing severe hyperparathyroid bone disease or disease on preexisting conditions of bone volume loss (postmenopausal osteoporosis or corticosteroid use) would be different (and likely more fragile with increased fractures) than newly diagnosed bone disease due to hyperparathyroidism.

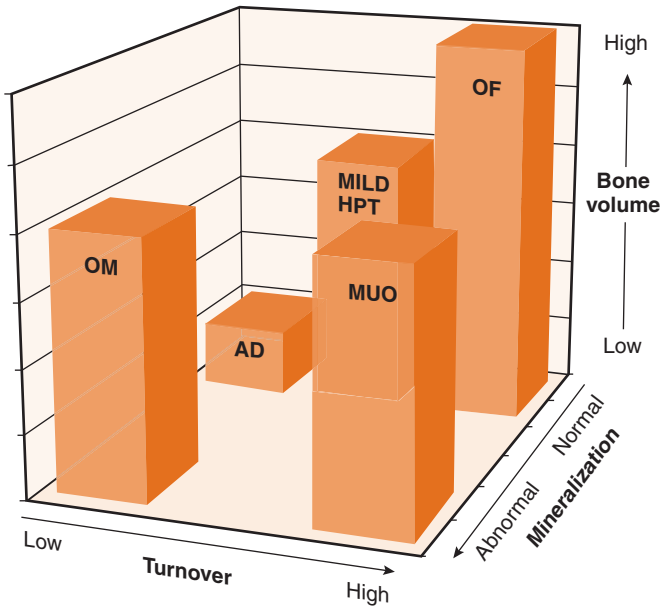


FIGURE 8-5 TMV classification system for bone histomorphometry. The figure is a graphical example of how the TMV system provides more information than the present, commonly used classification scheme. Each axis represents one of the descriptors in the TMV classification: turnover (from low to high), mineralization (from normal to abnormal), and bone volume (from low to high). Individual patient parameters could be plotted on the graph, or means and ranges of grouped data could be shown. For example, many patients with renal osteodystrophy cluster in areas shown by the bars. The OM *bar* (osteomalacia) is currently described as low-turnover bone with abnormal mineralization. The bone volume may be low to medium, depending on the severity and duration of the process and other factors that affect bone. The AD *bar* (adynamic bone disease) is currently described as low-turnover bone with normal mineralization, and the bone volume in this example is at the lower end of the spectrum, but other patients with normal mineralization and low turnover will have normal bone volume. The Mild HPT *bar* (mild hyperparathyroid-related bone disease) and OF *bar* (osteitis fibrosa or advanced HPT bone disease) are currently used distinct categories, but in actuality represent a range of abnormalities along a continuum of medium to high turnover, and any bone volume depending on the duration of the disease process. Finally, the MUO *bar* (mixed uremic osteodystrophy) is variably defined internationally. In the present graph, it is depicted as high-turnover, normal bone volume, with abnormal mineralization. In summary, the TMV classification system more precisely describes the range of pathologic abnormalities that can occur in patients with CKD. (From S. Moe, T. Drueke, J. Cunningham, et al., Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes [KDIGO], Kidney Int. 69 [2006] 1945-1953.)

VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE

Extraskeletal calcification can occur in multiple locations in patients with CKD: the cornea, areas around joints, pulmonary system, cardiac system, and the best characterized, vascular system. The high prevalence of vascular calcification in CKD patients is an old observation that has recently gained added attention due to new imaging modalities and increased understanding that the process is cell mediated. Ibels and colleagues in 1979[105] demonstrated that both the renal and internal iliac arteries of patients undergoing a kidney transplant had increased atheromatous/intimal disease and increased calcification compared to transplant donors. In addition, the medial layer was thicker and more calcified in the recipients compared to the donors.[105] A more recent study compared histological changes in coronary arteries from dialysis patients to those of age matched, nondialysis patients who had died from a cardiac event.[106] This study found a similar magnitude of atherosclerotic plaque burden and intimal thickness in the dialysis patients compared to controls, but with more calcification. In addition, morphometry of the arteries demonstrated increased medial thickening.[106] When these same authors evaluated more distal segments of the coronary arteries, they found medial calcification adjacent to the internal elastic lamina.[107]

The pathogenesis of arterial calcification is complex, but it appears that dedifferentiation of vascular smooth muscle cells to osteoblastlike cells is a major initiating factor. Elevated phosphorus, uremic serum, hyperglycemia, oxidative stress, inflammatory cytokines, and other so-called nontraditional cardiovascular factors appear to initiate this transformation.[71] Once the vascular smooth muscle cells are osteoblastlike, they appear to mineralize in a manner similar to bone, with the net calcification determined by the balance of promineralizing factors such as elevations in calcium and phosphorus and antimineralizing effects of circulating and local inhibitors such as fetuin-A and matrix gla protein.[71,108] Patients with CKD have elevations of calcium and phosphorus, and they have low levels of the circulating inhibitor fetuin-A due to increased inflammation.[109] Low levels of fetuin-A are associated with vascular calcification and increased mortality in patients with CKD.[110,111]

Vascular calcification has become easier to document with the advances in imaging in the recent decade, including electron beam computerized tomography (CT), spiral CT, and duplex ultrasonography. These techniques are thought to be more reproducible than the older method of observing progression of vascular calcification on plain radiographs. Electron beam CT and spiral CT allow rapid imaging of the heart in diastole, such that calcification in the coronary arteries can be easily distinguished and quantified. In 1996 Braun and colleagues found that hemodialysis patients had twofold to fivefold greater coronary artery calcification than age-matched individuals with normal kidney function that had angiographically proven coronary artery disease.[112] Goodman and colleagues subsequently demonstrated that advanced calcification can also occur in the coronary arteries of children and young adults on hemodialysis and is related to increased doses of calcium-containing phosphate binders, and increased

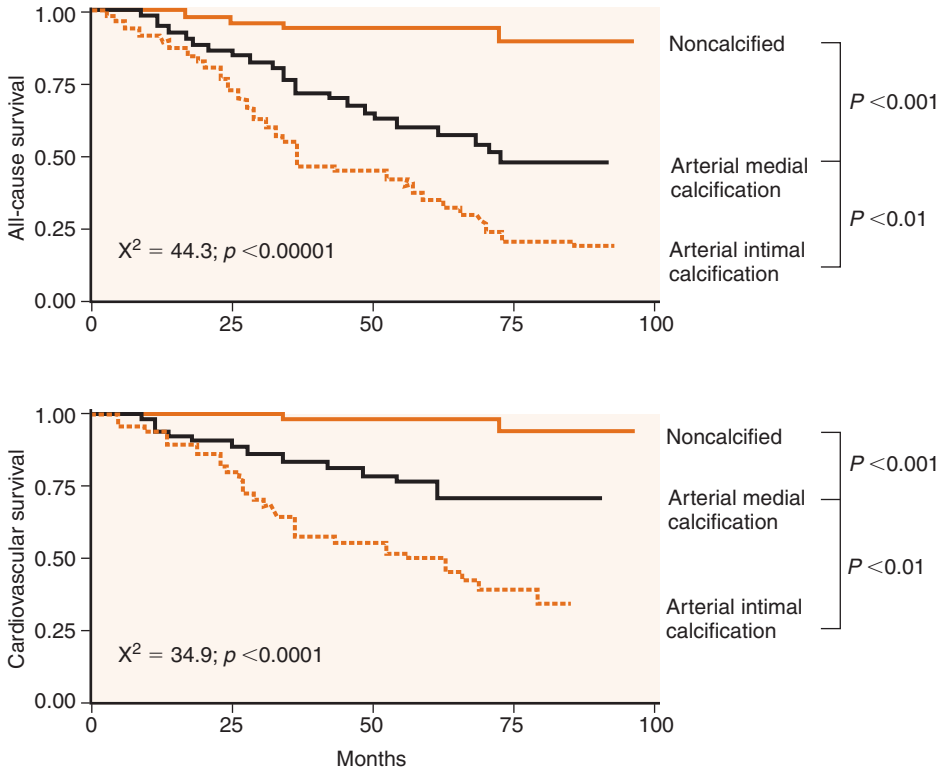


FIGURE 8-6 Peripheral artery calcification. Plain radiographs of the thigh demonstrate calcification of the femoral artery in a plaquelike arrangement (termed intimal) or a medial (circumferential) arrangement. Using these radiographs, patients were classified into medial or intimal (including mixed medial and intimal lesions) or no calcification, and followed prospectively. There was lowest survival for patients with intimal calcification, followed by medial calcification, followed by no calcification. (From G.M. London, A.P. Guerin, S.J. Marchais, et al., Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality, Nephrol. Dial. Transplant. 18 [2003] 1731-1740.)

calcium-phosphorus product.[113] Data in patients with CKD not yet on dialysis also demonstrate an increased risk of coronary artery calcification, especially in those with diabetes.[114] Nearly 50% to 60% of patients starting hemodialysis have evidence of coronary artery calcification,[115] and most series describing prevalent hemodialysis patients find 70% to 80% of all patients have evidence of coronary artery calcification.[116] The only risk factors for coronary artery calcification that are uniform across studies are advanced age and duration of dialysis. Mineral metabolism abnormalities including hyperphosphatemia, elevated calcium-phosphorus product, or excessive calcium load from phosphate binders have been identified as additional risk factors in several, but not all, studies.[117]

In the general population, coronary artery calcification is predictive of future cardiac events in both asymptomatic and symptomatic individuals.[118,119] Less robust data exist for CKD patients. Two small studies have demonstrated an increase in mortality with increased coronary artery calcification.[120,121] Importantly, a larger prospective study followed 114 patients who were new to dialysis and showed that a baseline electron beam computed tomography (EBCT) calcification score of more than 400 was associated with a 16-fold increase in mortality.[122] Increased valvular calcification in CKD patients is also associated with increased mortality.[123] Interestingly, small studies suggest that nocturnal dialysis[124] and kidney transplantation[120] appear to stabilize the progression of coronary artery calcification.

Peripheral artery calcification is also common in patients with CKD.[125] Dialysis patients with intimal calcification of the femoral artery by plain radiograph had increased all-cause and cardiovascular mortality compared to those with medial calcification, which in turn is significantly greater than in those with no medial calcification (Figure 8-6).[126] These data have been duplicated in multiple studies using hand and pelvic radiographs, abdominal scans, and other plain radiographic imaging studies.[126,127] Calcification of the larger arteries is associated with reduced baroreflex sensitivity[128] and increased pulse wave velocity and pulse pressure.[127] Of note, increased pulse wave velocity[129] and pulse pressure[130] are associated with increased mortality. Alterations in mineral metabolism appear to be associated with increased calcification in peripheral arteries in the majority of studies.[125]

There is an inverse relationship of bone mineralization and vascular calcification. The ability of bone to mineralize appears to peak at age 25 to 35 years old. Thereafter, bone mineral content decreases gradually, with a 5-year acceleration at the time of menopause in women. These age-related changes appear to be elevated in patients with kidney disease. Interestingly, coronary artery calcification progresses from the age of 25 to 35 until death.[71] A cross-sectional study of dialysis patients found a significant inverse correlation between coronary artery calcification by EBCT and bone mineral density by CT.[112] It appears that low turnover bone disease accounts for the greatest risk of vascular calcification of these patients.[131] Studies of patients who had undergone bone biopsy showed that those with the lowest PTH and lowest bone turnover on biopsy had the greatest arterial calcification by ultrasound[132] and more aortic stiffness.[133] Barreto and colleagues found over a 1-year period that patients with persistent low turnover bone disease were more likely to have progression of their coronary artery calcification.[44] The likely mechanism for these findings is that adynamic bone cannot incorporate an acute calcium load, whereas actively

remodeling bone can.[41] Additional evidence of the relationship of vascular calcification and osteoporosis has been gained from studies in the general population and knockout mouse models (reviewed in Moe and Chen[71] and Moe[134]).

ESTABLISHING A NEW PARADIGM: CHRONIC KIDNEY DISEASE-MBD

As is evident from the previous discussion, patients with CKD develop abnormalities in the serum levels of phosphorus, calcium, PTH, and vitamin D. The bone changes that ensue are associated with these biochemical alterations and other mechanisms. Both the biochemical changes and bone abnormalities contribute to vascular calcification. All three of these processes are closely interrelated and account for the significant morbidity and mortality of patients with CKD, and they form the rationale for the newly named syndrome CKD-MBD.[1]

Management of Chronic Kidney Disease-MBD

Clinical Practice Guidelines

Clinical practice guidelines are tools to help translate research advances into practice. They are used by clinicians, and also by insurance providers, governments, the United States Food and Drug Administration, and other regulatory agencies to establish standards of care for clinical practice. They are usually developed through a series of steps and are led by an evidence review team and a panel of experts. These individuals define the populations, predictors, interventions, and outcomes of interest and develop literature search strategies. The evidence review team then grades the quality of evidence for the outcomes of each study and provides an overall quality of evidence. The work group then writes recommendations and grades the strength of that recommendation. In CKD, the largest series of evidence-based guidelines are from the National Kidney Foundation Kidney Disease Quality Outcome Initiative (K/DOQI; www.kidney.org/professionals/KDOQI). The Bone and Mineral Guidelines were published in 2003.[43] In these guidelines, the first in this field in the United States, the majority of the recommendations were opinions of the work group due to the lack of strong evidence. Several other countries have simultaneously developed additional guidelines. KDIGO (Kidney Disease Improving Global Outcomes; www.kdigo.org) was developed to provide global clinical practice guidelines such that standards of care could be worldwide and to save the cost of the evidence review in every country that wished to develop guidelines. The process of developing guidelines and grading the level of evidence is under evaluation by multiple international organizations. KDIGO adapted a GRADE criteria,[135] that had more explicit definitions of how to grade the quality of the evidence than did the earlier K/DOQI guidelines. KDIGO guidelines have the following system: A two tier system (1 and 2) corresponding to strong and weak for the strength of the recommendation, and a four level system for the quality of the evidence (A = high, B = moderate, C = low, D = very low). Similar to the K/DOQI guidelines, the KDIGO guidelines on CKD-MBD from 2009[69] found a paucity of high quality evidence that focused on patient level outcomes. As such, the majority of recommendations are level 2. In addition, the KDIGO guidelines on CKD-MBD set higher standards for inclusion of treatment studies than K/DOQI. Despite these key differences, the final KDIGO recommendations are very similar with the exception of eliminating the tight PTH targets. These two guidelines are compared in Table 8-2. The remainder of this chapter discusses some of the studies that led to these recommendations. Unfortunately, high-quality, randomized, controlled clinical trials with patient level outcomes are lacking in this field. Furthermore, CKD-MBD is unique to CKD, and thus we cannot easily extrapolate from the general population.

Phosphate Control in Chronic Kidney Disease

Hyperphosphatemia plays a role in the pathogenesis of secondary hyperparathyroidism by directly suppressing PTH secretion and has an indirect effect by inhibiting the activation of calcitriol. Hyperphosphatemia also contributes to the downregulation of the vitamin D receptor (VDR) in the parathyroid gland (and perhaps also in bone).[23] Phosphorus also upregulates RUNX2 (Cbfa1), which is an "osteoblast's" transcription factor that transforms vascular smooth muscle cells to an osteoblast phenotype capable of mineralizing, and thus contributing to vascular calcification.[136] Lastly, phosphorus increases FGF-23 secretion from osteoblasts. Thus, hyperphosphatemia is at the core of several derangements observed in patients with CKD-MBD; therefore, normalizing phosphorus is an important therapeutic goal for CKD-MBD. Unfortunately, it remains challenging and requires a combination of dietary restriction, phosphate binders, and enhanced dialytic removal.

Diet Phosphorus is an inherent element in plant and animal cells; however, the content of phosphorus in protein foods and the proportion that can be absorbed vary greatly. For instance, plant sources of food are high in phosphorus, but the enzyme phytate is required for the breakdown of ingested phosphorus, and because this enzyme is absent in humans, phosphorus absorption of proteins derived from plant foods is less complete. Phosphorus is also added to processed foods including meats, spreads, puddings, caramelized colas, and many of the "fast foods" and less expensive foods. Foods processed with polyphosphates and pyrophosphates are rapidly absorbed. A randomized trial found that counseling dialysis patients to avoid processed foods can reduce the serum phosphorus.[2] Dietary phosphorus restriction has been shown to prevent the development of secondary hyperparathyroidism in animal studies.[137] Thus, there is strong rationale to restrict dietary phosphorus intake in early stages of CKD, and limiting intake may make binders more efficacious in late stages of CKD.

The NKF K/DOQI[43] guidelines suggest that dietary phosphorus be restricted in patients at all stages of CKD to 800 to 1000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated above the normal range or when the serum PTH levels are above target range (opinion). Although the theoretical and experimental data demonstrating that this prevents the development of secondary hyperparathyroidism are compelling, definitive evidence of sustained efficacy of dietary phosphorus restriction in preventing or treating secondary hyperparathyroidism in humans is lacking. Despite this

TABLE 8-2 Overview of K/DOQI versus KDIGO Clinical Practice Guidelines

	K/DOQI	KDIGO
Methodology	Evidence review by external evidence review team (ERT) with additions from work group	Evidence review by external ERT with additions from work group
Grading of Statements	Evidence or opinion Evidence subjective determination by work group without predefined criteria Focus on all outcomes	Adaptation of Grade: Strength of recommendation: strong or weak (level 1 and 2) and quality of evidence (high = A, moderate = B, low = C, very low = D) Focus on patient centered outcomes
Entry Criteria for Use of Treatment Studies	Evaluated all types of studies, minimum number was 10 patients per arm, except for crossover studies where 5 patients per arm were included.	Used only RCTs with a priori determined criteria: trial duration greater or equal to 6 months and minimum number of 50 patients, except for studies of bone outcomes, which required a minimum number of 20 patients
Laboratory Tests Stage 5D	Target values given for CKD 5D: Phosphorus < 5.5 mg/dl (evidence) Calcium < 10.5 mg/dl (opinion) PTH 150 to 300 pg/ml (evidence)	No specific targets given for CKD 5D: Phosphorus: "lower towards normal" (2C) Calcium: normal range (2D) PTH: > 2 and < 9 times the upper limit for the assay, address major changes in trends in PTH within that range (2C)
Laboratory Tests Stage 3-5	Normal values for phosphorus and calcium (evidence) Intact PTH <70 for CKD stage 3, Intact PTH < 110 for CKD stage 4 (both opinion)	Normal values for phosphorus (2C) and calcium (2D) Ideal level of PTH for this stage of CKD unknown—avoid progression (2C). All patients use trends rather than isolated values.
Phosphate Binder Choices	Stage 3-4 CKD: calcium (opinion) Stage 5 CKD: any binder for control of phosphorus; limit elemental calcium intake to 1500 mg from binder, noncalcium if PTH < 150 pg/ml or vascular calcification (opinion)	Stage 3-4: no preference given Stage 5: No preference for binder (2B). Limit calcium intake from binders if low PTH or adynamic bone disease or vascular calcification (2C)
Treatment of Elevated PTH	Stage 3-4: if vitamin D deficient, replete. Otherwise "active" vitamin D (opinion) Stage 5D: No difference in calcitriol or vitamin D analogs (evidence), use of latter in refractory hypercalcemia (opinion)	Stage 3-4: if PTH elevated treat vitamin D deficiency, hypocalcemia and hyperphosphatemia (ungraded). If continues to rise, use calcitriol or vitamin D analog (2C). Stage 5D: Use calcitriol, vitamin D analog, and/or calcimimetics (2B) with choice dependent on calcium and phosphorus levels.

K/DOQI, Kidney Disease Outcomes Quality Initiative;[43] *KDIGO*, Kidney Disease Improving Global Outcomes[69]

limitation, designing programs that educate patients about the different content and absorptive properties of phosphorus-containing foods may be a worthwhile adjunct to the management of serum phosphorus levels with binder therapy.

Phosphate Binders The use of aluminum as a phosphorus binder was popular throughout the 1970s and 1980s. But as evidence emerged implicating aluminum's role in osteomalacia and dialysis encephalopathy, the therapeutic trend shifted to the use of high-dose calcium carbonate. In the decade that followed, it was noted that calcium acetate would reduce the elemental load of calcium while controlling the serum phosphorus level when compared to calcium carbonate, although there was no difference in the incidence of hypercalcemia.[138] Subsequent studies demonstrated that the calcium-containing phosphate binders were associated with increased burden of vascular calcification in some, but not all studies.[116,117] This and the increased risk of hypercalcemia with the concomitant use of vitamin D led to a need for noncalcium-containing, nonaluminum-containing phosphate binders. In 1998, sevelamer hydrochloride (HCl) was introduced and was shown to be as effective as calcium acetate in maintaining the serum phosphorus without hypercalcemia in crossover trials.[139,140]

In a nonblinded study called the "Treat-to-Goal" study, patients were randomized to either a calcium-based binder or sevelamer HCl for 1 year. Despite equivalent phosphorus control, patients taking a calcium binder had progression in coronary and aorta calcification by EBCT, whereas patients treated with sevelamer HCl did not progress.[141] In an open label extension of this study in Europe for a second year, EBCT scores continued to rise significantly in patients treated with a calcium-based binder, but not in the sevelamer HCl group.[142] The Renagel in New Dialysis Patients (RIND) study[115] found that approximately 65% of patients new to dialysis have coronary artery calcification. In this 18-month trial, 60 incident hemodialysis patients were randomized to calcium-based binders and 54 to sevelamer HCl . Similar to the Treat-to-Goal study, patients had equivalent control of serum phosphorus levels, yet patients treated with calcium-based binders had progressive calcification and those treated with sevelamer HCl did not.[115] In a study of 90 binder-naive patients with CKD stages 3 to 5 who were not receiving dialysis, Russo and colleagues randomized patients (30 per group) to either a low-phosphate diet alone, a low-phosphate diet in combination with fixed doses of calcium carbonate (2 g/day), or a low-phosphate diet in combination with sevelamer HCl (1600 mg/day), and they followed these individuals for 2 years.[143] The primary endpoint of the study was progression of coronary artery calcification, assessed as the total calcium score using multislice spiral CT. Among the 84 patients who completed the study, final coronary artery calcification scores were greater than initial scores in those receiving diet alone ($P < 0.001$) or diet in combination with calcium carbonate ($P < 0.001$), whereas there was no progression of calcification in the group treated with diet plus sevelamer HCl.[143] Thus, three studies found less calcification with the use of sevelamer HCl compared to calcium-based binder.

Two studies have failed to find differences in coronary artery calcification with sevelamer HCl compared to calcium-based binders. In the CARE 2 study, chronic hemodialysis patients from the United States were randomized to receive either calcium acetate or sevelamer HCl.[144] The hypothesis was that the addition of a statin to the patients being treated with a calcium binder would lead to equivalent coronary artery calcification to sevelamer HCl alone. Subjects in both groups received atorvastatin to achieve an low-density lipoprotein goal of 70 mg/dl (1.82 mmol/L). The study was designed to assess noninferiority, evaluating coronary artery calcification by EBCT at 6 and 12 months after randomization. Before 1 year, 30% of patients in the sevelamer HCl arm and 43% in the calcium acetate arm dropped out, leaving the final sample size below the power needed to determine noninferiority. This drop out was similar to other studies. There was no difference in the progression of arterial calcification and similar lipid control. Of note, CARE 2 showed that the combination of sevelamer HCl and atorvastatin was associated with a much higher rate of progression of coronary artery calcification than in the Treat-to-Goal study.[141] The Brazilian Renagel and Calcium (BRIC) study compared calcium acetate versus sevelamer HCl on coronary artery calcification progression and bone histomorphometry in hemodialysis patients.[145] The primary goal of the study was to test the hypothesis that treatment with calcium-containing phosphate binders has a negative impact on bone remodeling and that this contributes to a more rapid progression of coronary artery calcification than treatment with sevelamer HCl. The annual rates of progression of coronary calcification scores were not statistically different. However, this study was hampered by several significant confounders; differences in baseline coronary artery calcification scores between the two study arms; the use of high dialysate calcium concentrations in most patients; and multiple interventions during the course of the study allowed by the caring physicians based on bone biopsy results. Thus, two studies failed to find that sevelamer HCl had beneficial effects on coronary artery calcification compared to calcium-based phosphate binders.

Two studies have examined the effect of sevelamer HCl, compared to calcium-based binders, on mortality. The largest of these studies, the Dialysis Clinical Outcomes Revisited (DCOR), randomized 2103 prevalent CKD stage 5D patients to either sevelamer HCl or a calcium-based phosphate binder (70% calcium acetate or 30% calcium carbonate).[146] The trial was designed to evaluate all-cause mortality as the primary endpoint and had 80% power to detect a 22% difference between the groups. The study had a high early discontinuation rate with an overall dropout rate of 47% in the sevelamer HCl arm and 51% in the calcium-based binder arm. Patients received standard of care from their doctors, who were not blinded to the treatment. The study duration was extended because the mortality rate in the control group was lower than expected. Only 1068 patients completed the study, and there were no differences in all-cause or cause-specific mortality rates when comparing sevelamer HCl (mortality rate 15 per 100 patient-years) with calcium-treated patients (16.1 per 100 patient-years) (hazard ratio 0.93, 95% confidence interval 0.79 to 1.1, log rank $P = 0.4$). A subgroup analysis of patients over 65 years of age (a prespecified analysis) and those receiving treatment for more than 2 years (secondary analysis) did show benefit in mortality rate. A secondary preplanned analysis of the DCOR study using Medicare claims data (rather than data collected at the study sites on case report forms) demonstrated no effect on mortality, cause-specific mortality, morbidity, or first or cause-specific hospitalization.[147] This study did demonstrate a beneficial effect of sevelamer HCl on the secondary outcomes of multiple all-cause hospitalizations (1.7 versus 1.9 admissions per patient year, $P = 0.02$) and hospital days (12.3 versus 13.9 days per patient-year, $P = 0.03$). Thus, both analyses showed lower hospitalization rates with sevelamer HCl, but no difference in mortality.[147] The very high dropout rate made the study underpowered; thus, it should not be considered a negative study, but rather an inadequate study.

The second study examining clinical outcomes was the RIND. This study randomized a smaller group of 148 hemodialysis patients new to dialysis to either sevelamer HCl or calcium-based binder, and it followed these patients for a longer period. Only 127 patients received baseline EBT scans, and the dropout rate was 26% in the sevelamer HCl arm and 27% in the calcium-based phosphate binder arm. At a median of 44 months, by multivariate analysis, there was a difference in adjusted mortality rates for patients assigned to calcium-containing binders (10.6 per 100 patient-years, confidence interval 6.3 to 14.9) compared to mortality rates for patients assigned to sevelamer HCl (5.3 per 100 patient-years, confidence interval 2.2 to 8.5) (hazard ratio 3.1, $P = 0.016$). Thus, there are conflicting data on mortality benefits of sevelamer HCl compared to calcium-based binders, and more research is needed.

Another noncalcium binder, lanthanum carbonate was introduced in 2005. Lanthanum carbonate effectively binds intestinal phosphorus without sequestering bile acids and is poorly absorbed. The tablets are chewable and well-tolerated. Randomized prospective studies have demonstrated that lanthanum carbonate controls serum phosphorus and other binders, but with less hypercalcemia.[148–150] Although there has been concern of toxicities similar to aluminum, the clearance of lanthanum is primarily by the liver as opposed to renal clearance for aluminum. Although animal studies are controversial, in human studies no liver toxicity, suppression of erythropoiesis, or change in the mental status examination have been observed.[150] In addition, no direct bone toxicity has been demonstrated. In a randomized, open-label, multicenter study where bone biopsies were performed, lanthanum did not induce osteomalacia, whereas treatment with calcium carbonate increased the incidence of adynamic bone disease.[151–153] To date, there are no human studies demonstrating that lanthanum carbonate can prevent vascular calcification.

The K/DOQI Guidelines for bone metabolism and disease[43] predated the publication of the Treat-to-Goal study, RIND, CARE 2 study, and the availability of lanthanum. The K/DOQI guidelines recommend that the use of calcium binders be limited to a maximum intake of 1500 mg/day of elemental calcium (about three calcium carbonate and nine calcium acetate tablets per day). The total maximum elemental calcium intake from both binders and diet should not exceed 2000 mg/day. The guidelines also recommend that a calcium-based binder not be used when there is hypercalcemia (serum calcium above 10.2 mg/dl or 2.55 mmol/L) and when the PTH is below 150 pg/ml (16.5 pmol/L). The latter recommendation is because of data demonstrating

TABLE 8-3 Comparison of Different Phosphate Binders

	ALUMINUM	CALCIUM	MAGNESIUM	LANTHANUM	SEVELAMER
Efficacious	✓✓✓	✓✓	✓✓	✓✓✓	✓✓
Absorbed	Yes	Yes	Yes	Yes	No
Accumulates	Yes	Yes	Yes	Yes	No
Hypercalcemia	No	Yes	No	No	No
K/DOQI and KDIGO Restrictions	Yes	Yes	Not mentioned	No	No
Lipid effect	No	No	No	No	Yes
Endpoints other than serum phosphorus levels	Yes: CNS and bone toxicity	Yes: Mixed studies on coronary artery calcification; suppresses bone remodeling	No	Yes: No adverse effect on bone	Yes: Mixed studies on coronary artery calcification; one study positive and one indeterminate in improved mortality

✓relative potency.

that low turnover bone cannot appropriately incorporate a calcium load, thereby increasing the risk for extraskeletal calcification.[41,44,132,133] The KDIGO guidelines have similar recommendations to limit calcium binder intake in patients with hypercalcemia, arterial calcification, and evidence of adynamic bone disease, although it was felt that there were insufficient data to warrant a specific threshold. Both guidelines note the lack of clear evidence for these recommendations; thus, they are based on expert consensus. Furthermore, the KDIGO guidelines state that one binder cannot be clearly recommended over another due to the lack of definitive data on patient centered endpoints.

A comparison of the phosphate binders is given in Table 8-3. In clinical practice, economic factors, patient preference, and gastrointestinal distress limit adherence to a rigorous diet and binder schedule. By combining some of the various binders to minimize side effects, achieving phosphorus control is more likely. In the end, the best phosphate binder is what works for an individual patient. Ultimately, there are no studies that demonstrate that lowering the phosphorus level to a specific level improves mortality; thus, while a normal phosphorus level is a reasonable goal in most patients, the clinician must consider the potential adverse events of the binders in a given patient.

Improved Dialytic Clearance of Phosphorus Conventional dialysis removes 1000 mg of phosphorus per dialysis, but because 1000 mg is absorbed on a daily basis, the net positive balance may be 4,000 mg per week.[138] Patients who undergo nightly dialysis have weekly removal of phosphate that is twice as high. In a study of 10 patients dialyzing 8 to 10 hours, 6 to 7 days per week at blood flows of 100 ml/min/1.73 m^2, it became possible to discontinue binder therapy and increase dietary phosphate (and protein) intake.[154] One prospective, randomized, controlled trial has reported the impact of alternative dialysis therapies using biochemical markers of CKD-MBD as a secondary endpoint.[155] In this study, 26 patients receiving nocturnal, prolonged-duration, hemodialysis six times weekly were compared to 25 patients receiving standard hemodialysis given three times weekly for 4 hours each session in a parallel design. The authors found significant decreases in serum phosphorus and intact PTH, but no difference in calcium in the patients allocated to frequent nocturnal hemodialysis. Importantly, the phosphate-binder dose was also reduced. These data suggest that frequent nocturnal hemodialysis can lead to an improvement in mineral metabolism. Thus, optimized control of serum phosphorus may require use of alternative dialytic regimens in addition to diet and phosphate binders in some patients.

Control of Parathyroid Hormone

In the setting of CKD, PTH is increased in response to hyperphosphatemia, low calcitriol, and elevated FGF-23. Most series demonstrate that at least 50% of patients on dialysis have secondary hyperparathyroidism, and in many series the prevalence is far greater.[77] In addition to increased secretion of PTH, there is altered degradation and resistance to its skeletal effects. As a result, levels of PTH are uniformly increased compared to the general population, and yet levels two to five times the upper limit for the general population may be associated with decreased bone turnover in CKD patients. Although PTH affects multiple organ systems, the focus over the last 20 years has been on bone, and PTH had become a surrogate marker for bone turnover. Unfortunately, recent data do not support that assumption, and the KDIGO guidelines based the optimal levels of PTH on associations of PTH with mortality.

Treatment of Elevated PTH: Patients with Chronic Kidney Disease Stages 3 and 4 In CKD stages 3 and 4, the ideal PTH level is unknown. It is also likely that someone who presents in stage 4 with an elevated PTH that is suppressed to normal with therapy is very different from someone who has been followed longitudinally and has never progressed to have an elevated PTH. Put simply, it is not clear at what point normal homeostatic increases in PTH become maladaptive. However, it is known that severe nodular secondary hyperparathyroidism is harder to treat; thus, progressive hyperparathyroidism should be reversed. The KDIGO guidelines recommend treating hypocalcemia, hyperphosphatemia, and vitamin D deficiency to attempt to reverse the disease process. Although calcium has been used for a long time to suppress PTH, studies are inadequate to assess potential side effects, especially arterial calcification. Treatment of hyperphosphatemia to lower PTH is theoretically important, but again data are limited. A recent 8-week study in patients with CKD stages 3 to 4 with hyperphosphatemia found a decrease in PTH in patients treated with lanthanum compared to placebo.[156]

The use of nutritional vitamin D (ergocalciferol or cholecalciferol) has also only received limited research. A posthoc analysis of the Vitamin D, Calcium, Lyon Study II (DECALYOS II) was conducted by Kooienga and coworkers.[157] This study assessed the impact of treatment with cholecalciferol 800 International Units plus calcium 1200 mg daily versus placebo on biochemical parameters in 610 elderly French women, of whom 322 had eGFR values less than 60 ml/min/1.73 m^2 using the MDRD formula. The treatment with vitamin D raised serum levels and lowered PTH in the study, and there was a similar response in individuals with eGFR less than 45 ml/min/1.73 m^2, less than 60 ml/min/1.73 m^2, and greater than 60 ml/min/1.73 m^2 compared to placebo ($p < 0.001$ for all). However, this study was unable to distinguish between effects of calcium and vitamin D because these treatments were given in combination.[157] In CKD 3 and 4 patients with vitamin D (25 [OH]D) levels less than 30 ng/ml and elevated levels of PTH, an observational treatment study using ergocalciferol reported normalization of mean 25(OH)D levels in both CKD stages.[158] Significant reduction in median levels of PTH was seen in patients with CKD 3, with a trend to reduced median PTH levels in CKD 4.[158]

The KDIGO[69] guidelines further recommend that if the PTH level continues to rise in patients with CKD stages 3 and 4, calcitriol or vitamin D analogs can be used to suppress PTH. Four randomized controlled trials of greater than 6 months duration exist, and they compare placebo to doxercalciferol (n = 55 patients[39]), paricalcitol (n = 220 patients[159]), alfacalcidol (n = 176 patients[160]), or calcitriol (n = 30 patients[161]). All studies assessed laboratory values and demonstrated superior efficacy for suppression of PTH compared to placebo. The Hamdy and Nordal papers also evaluated bone histology and found improved bone turnover in the treatment groups. There are no comparative studies of different forms of vitamin D to each other nor are there any studies that assess patient level outcomes. There is one study using calcimimetics to treat hyperparathyroidism in patients with CKD 3 and 4. In this trial, the calcimimetics lowered the PTH effectively compared to placebo, but they also lowered the calcium and raised the phosphorus.[162] Given the concerns over hyperphosphatemia, unless patient level outcome studies are performed this agent should be reserved for patients on dialysis. Thus, much research is needed in this population.

Treatment of Elevated PTH in Chronic Kidney Disease Stage 5D: Calcitriol and Vitamin D Analogs The use of calcitriol has been the key to the management of hyperparathyroidism for nearly 30 years; however, a common side effect has always been hypercalcemia. Initially, the higher level of serum calcium was thought to be a therapeutic advantage, providing additional PTH-suppressive effects independent of vitamin D. However, as hypercalcemia became a concern, new vitamin D analogues were designed to maximize PTH suppression yet minimize intestinal absorption of calcium and phosphate. Two "less calcemic" analogs are commercially available in the United States: 19-nor-1,25$(OH)_2D_2$ (paricalcitol) and 1α$(OH)D_2$ (doxercalciferol), and others are available outside the United States.[163] All of these analogs appear effective in suppressing hyperparathyroidism in patients on dialysis.[164–170] Paricalcitol appears superior to calcitriol in terms of its hypercalcemic and hyperphosphatemic effects in comparison studies in rats[171] but human data are lacking. A secondary analysis of a trial comparing paricalcitol and calcitriol has been published. This study found that although there was no difference between paricalcitol and calcitriol in the number of subjects who had a single episode of hypercalcemia, paricalcitol led to less sustained hypercalcemia.[172] There are no published direct comparative trials of doxercalciferol to paricalcitol, or doxercalciferol to calcitriol. In addition, there are no prospective studies evaluating patient level endpoints, and only limited bone studies.[173] The lack of comparative trials makes blanket endorsement of preferential use of any of these analogs over calcitriol premature, and the KDIGO guidelines could not recommend one agent over another.[69] More recent attention has focused on the potential positive effects of these analogs on survival in dialysis patients, apparently independent of their effects on calcium, phosphorus, and PTH. Retrospective analyses demonstrate a survival advantage in patients receiving any form of vitamin D compared to no vitamin D, with paricalcitol and doxercalciferol having superior survival advantage over calcitriol.[74,84,174,175] However, these results must be confirmed in prospective trials as one cannot completely control for the bias of the decision to use vitamin D in a given patient.

Treatment of Elevated PTH in Chronic Kidney Disease Stage 5D: Calcimimetics Calcimimetics are a group of drugs that are allosteric activators of the calcium-sensing receptor, thereby enhancing signaling and decreasing PTH release independent of vitamin D.[176] The only calcimimetic commercially available is cinacalcet HCl. In the initial studies, this agent proved effective in suppressing PTH, but with some hypocalcemia.[177] The phase II trials demonstrated suppression of PTH and lowering of both calcium and phosphorus, leading to a reduction in the calcium x phosphorus product.[178] Phase III data confirm these results.[179] Composite data from all phase 3 studies in over 1100 patients around the world demonstrated that the use of this agent can lead to suppression of PTH with a lowering of the calcium x phosphorus product,[180] allowing achievement of the current K/DOQI guidelines in many more patients that current regimens. Long-term studies have demonstrated continued efficacy.[181] A retrospective review of phase III data demonstrated a benefit of patients treated with cinacalcet on reduced hospitalization, reduced fractures, and a trend toward reduced mortality.[182] The ability of calcimimetics to lower both calcium and phosphorus differentiates this agent from calcitriol and vitamin D analogs that raise the calcium x phosphorus product. There is a large prospective international mortality study underway to compare the calcimimetic cinacalcet to standard of care, which generally includes vitamin D, with results expected in the year 2012.

At this point, the KDIGO guidelines[69] recommend that calcitriol, vitamin D analogs, or calcimimetics can be used in CKD stage 5D to lower PTH, with the choice dependent on the serum calcium and phosphorus levels.

Treatment of Elevated PTH: Parathyroidectomy The need for parathyroidectomy to control secondary hyperparathyroidism should decrease as newer medications offer more flexibility with PTH control. However, patients with serum PTH levels greater than 1000 pg/ml that have been refractory to medical therapy have traditionally been considered candidates. This includes patients who cannot

receive vitamin D sterols due to an elevated calcium and those who do not tolerate cinacalcet secondary to gastrointestinal disturbances. A study found decreased mortality and lower risk of hip fractures in subjects who underwent parathyroidectomy compared to those who did not from the United States Renal Data System database.[183,184] While this type of data is biased by patient selection for parathyroidectomy, it raises a question about whether the procedure is delayed too long in some patients. Unfortunately, with PTH assays being so problematic, there is no specific level of PTH at which parathyroidectomy is currently recommended.

CONCLUSION

CKD-MBD is a systemic disorder of abnormal serum levels of mineral-related biochemistries, abnormal bone, and extraskeletal calcification. Although understanding of how these components are interrelated has advanced, the available therapeutic tools remain focused on only the biochemical abnormalities of CKD-MBD. However, the management of these disorders is also interrelated; drugs that may help one aspect of the disorder may cause or accelerate another. As such, management remains a major challenge and requires balancing risks and benefits of the various available therapies. An important challenge for the decade ahead is to determine which combinations of therapies can be used safely together to prevent morbidity and mortality in CKD. Furthermore, the pathophysiology that sets these events into motion begins long before the onset of ESRD. Therefore, earlier detection and management of CKD-MBD should be emphasized.

ACKNOWLEDGEMENTS

This chapter is dedicated to John and Michelle Moe for their unending support and patience. The author would like to thank Michelle Murray for her expert administrative support in the preparation of this chapter.

A full list of references are available at www.expertconsult.com.

VITAMIN D DEFICIENCY

Chapter 9

Ian H. de Boer, M.D., M.S.

The kidney plays a fundamental role in the metabolism of vitamin D. Humans obtain vitamin D (cholecalciferol and ergocalciferol) from cutaneous synthesis and dietary intake. These forms of vitamin D undergo regulated conversion to compounds with full hormonal activity, most importantly calcitriol. The rate-limiting step in the generation of calcitriol is performed by the enzyme 1-α hydroxylase. This occurs largely in the proximal tubule of the kidney. Thus, calcitriol deficiency is a well-recognized consequence of chronic kidney disease (CKD). Also widely recognized are the important effects of calcitriol deficiency on bone and mineral metabolism in CKD. These include hyperparathyroidism, renal osteodystrophy, and increased risk of fracture (see Chapter 8).

For a number of reasons, interest in vitamin D deficiency has recently broadened beyond bone and mineral metabolism. First, potential far-reaching pleiotropic effects of vitamin D have been identified. On the basis of these potential pleiotropic effects, vitamin D may help prevent cancer, inflammation, activation of the renin-angiotensin-aldosterone system, glucose intolerance, cardiovascular disease, initiation and progression of CKD, and mortality. Second, it is now recognized that deficiency of vitamin D (cholecalciferol and ergocalciferol) is highly prevalent among persons with and without CKD. Third, nonrenal synthesis of calcitriol has been described, suggesting that supplementation with cholecalciferol or ergocalciferol, in addition to or instead of calcitriol or its analogues may have beneficial effects among persons with CKD.

With these concepts in mind, this chapter describes current knowledge of the pathophysiology, epidemiology, consequences, and therapy of vitamin D deficiency in CKD.

PATHOPHYSIOLOGY

Vitamin D

Humans obtain vitamin D as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) (Figure 9-1). "Vitamin D" refers jointly to cholecalciferol and ergocalciferol, which differ by their carbon side chains (Figure 9-2). For healthy individuals, the predominant source of vitamin D is cutaneous synthesis of cholecalciferol.[1–4] Within keratinocytes, ultraviolet (UV) light (wavelength 290 to 315 nm, within the UVB range) stimulates the conversion of 7-dehydrocholesterol to previtamin D3, which is then quickly converted to cholecalciferol. It has been estimated that 5 to 10 minutes exposure of the arms and legs to direct sunlight leads to the production of up to 3000 international units of cholecalciferol, though this varies by time of day, season, latitude, and skin sensitivity.[2] During winter months at high latitude, particularly higher than 40 degrees north or lower than 40 degrees south, very little light in the 290 to 315 nm range reaches the surface of the

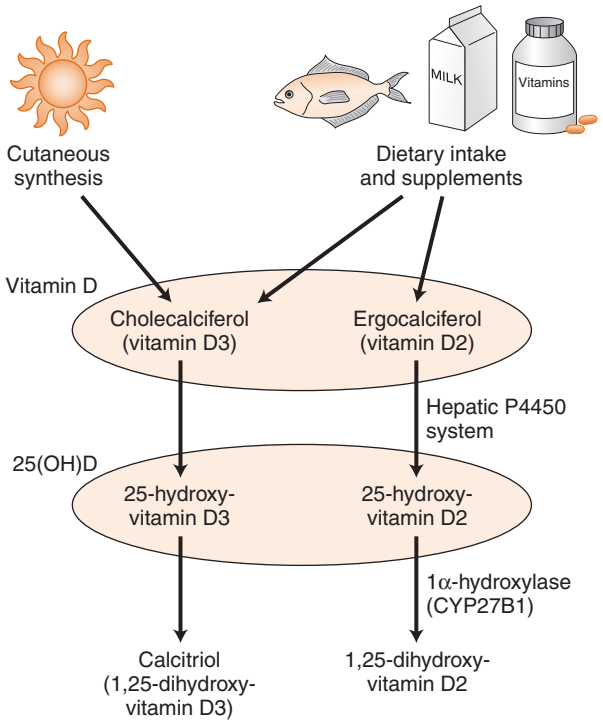


FIGURE 9-1 Sources and metabolism of vitamin D. *25(OH)D,* 25-hydroxyvitamin D.

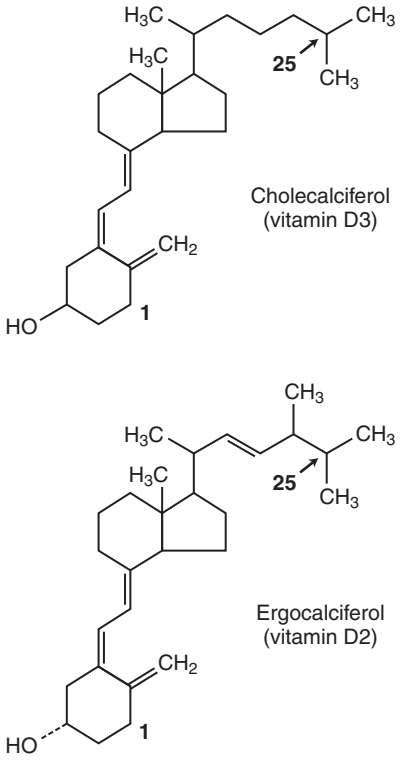


FIGURE 9-2 Chemical structures of cholecalciferol (vitamin D_2) and ergocalciferol (vitamin D_3). These two forms of vitamin D differ by their carbon side chain. The 1 and 25 carbons which require for hydroxylation for maximum hormonal activity are labeled.

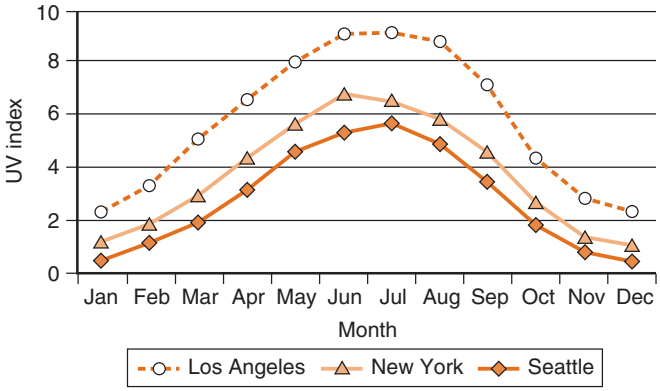


FIGURE 9-3 Mean monthly UV index for Los Angeles (latitude 34 degrees), New York (latitude 41 degrees), and Seattle (latitude 48 degrees). The *UV Index* is a next day forecast of the amount of skin damaging UV radiation expected to reach the earth's surface at the time when the sun is highest in the sky (solar noon). The amount of UV radiation reaching the surface is primarily related to the elevation of the sun in the sky, the amount of ozone in the stratosphere, and the amount of clouds present. To calculate the UV index, irradiances at 290 to 400 nm are weighted so as to reflect the human skin's response to each wavelength; weighting favors the wavelengths also required for cutaneous synthesis of vitamin D. Data presented are means for the calendar years 2000 to 2002, provided by the National Oceanic and Atmospheric Administration/National Weather Service.

earth (Figure 9-3), and cutaneous synthesis is markedly reduced. Sunlight destroys excess cutaneous cholecalciferol, so intense sun exposure does not cause vitamin D intoxication.

Vitamin D is also obtained from the diet and dietary supplements (Table 9-1).[5] Fatty fish provides the largest quantities of cholecalciferol, and milk is fortified with approximately 100 international units cholecalciferol per cup. Additional foods that sometimes contain supplementary cholecalciferol include other dairy products, orange juice, and breakfast cereals. Mushrooms produce ergocalciferol, and one serving of fresh shitake mushrooms contains approximately 100 international units. Vitamin D supplements are

TABLE 9-1 Selected Food Sources of Vitamin D

FOOD	INTERNATIONAL UNITS PER SERVING
Cod liver oil, 1 tablespoon	1360
Salmon, cooked, 3.5 ounces	360
Mackerel, cooked, 3.5 ounces	345
Tuna fish, canned in oil, 3 ounces	200
Sardines, canned in oil, drained, 1.75 ounces	250
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98
Margarine, fortified, 1 tablespoon	60
Ready-to-eat cereal, fortified with 10% of the daily value for vitamin D, 0.75–1 cup (more heavily fortified cereals may provide larger quantities)	40
Egg, 1 whole (vitamin D is found in yolk)	20
Liver, beef, cooked, 3.5 ounces	15
Cheese, Swiss, 1 ounce	12

available over the counter and by prescription. These contain cholecalciferol or ergocalciferol with a wide range of dose.

Vitamin D is fat soluble. More than 99% of circulating vitamin D is bound to plasma proteins, mostly vitamin D binding protein. Vitamin D binding protein circulates in substantial molar excess to its vitamin D ligands, with less than 5% of vitamin D-binding sites occupied under normal conditions.[6] Some vitamin D circulates bound to albumin, and vitamin D absorbed through the gut is also transported on chylomicrons. Storage of vitamin D and its metabolites in adipose tissue is important in intoxication and perhaps in moderation of seasonal fluctuations in cutaneous synthesis. However, the extent, location, and form of vitamin D storage in normal human physiology are not fully understood.

Calcitriol

Cholecalciferol and ergocalciferol have little inherent biological activity and require two hydroxylation steps for full hormonal potency. In the liver, cholecalciferol and ergocalciferol are converted to 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2, respectively. Together, these are referred to as 25-hydroxyvitamin D, or 25(OH)D (see Figure 9-1). With normal levels of vitamin D intake, 25(OH)D production by the hepatic cytochrome P450 system is proportional to substrate availability and is not rate-limiting. 25(OH)D is the major circulating form of vitamin D.

25-hydroxyvitamin D3 must be converted to calcitriol (1,25-dihydroxyvitamin D3) for maximal hormonal function. This is performed by the cytochrome P450 enzyme CYP27B1, or 1-α hydroxylase. The major site of 1-α hydroxylase activity is the proximal tubule of the kidney. 25-hydroxyvitamin D3 bound to vitamin D binding protein is filtered at the glomerulus, reabsorbed in the proximal tubule in a process facilitated by the luminal receptors megalin and cubilin, freed from vitamin D binding protein within lysosomes, and shuttled across the cytoplasm to mitochondria.[7] Here, conversion of 25-hydroxyvitamin D3 to calcitriol is tightly regulated by factors including serum phosphorous, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23).[8–10] 25-hydroxyvitamin D2 is converted to 1,25-dihydroxyvitamin D2 through parallel steps.

Most known actions of calcitriol require binding to the cytosolic vitamin D receptor. This receptor is similar in many ways to other nuclear receptors for steroids hormones.[11] Once ligand binding occurs in the cytoplasm, the calcitriol-vitamin D receptor complex must translocate to the nucleus, heterodimerize with the retinoid X receptor, bind to vitamin D response elements in the promoter regions of susceptible genes, and recruit coregulatory proteins to the site of binding. The result is upregulation or downregulation of the transcription of specific genes. Rapid actions of calcitriol, too fast to occur through altered gene transcription, have also been observed in animal models. This suggests the presence of a cell surface calcitriol receptor, which is currently believed to be a cell membrane-bound form of the vitamin D receptor.

The main pathway for calcitriol inactivation involves additional hydroxylation at carbon 23 or 24. These hydroxylation steps are catalyzed by specific enzymes that are present in virtually all target cells. In the kidney, 24-hydroxylase is regulated in a reciprocal manner to 1-α hydroxylase. Once hydroxylation occurs at carbon 23 or 24, further side chain cleavage leads to inactivation. Additional fates of calcitriol include formation of lactones and epimerization at the 3-α position.[11] 25(OH)D may be inactivated through the same pathways without conversion to calcitriol.

Disturbances in Chronic Kidney Disease

Vitamin D metabolism is profoundly disordered in CKD. Abnormalities begin during early CKD stages (prior to stage 3) and progress as renal function declines.[12] The central feature of this process is a decline in circulating calcitriol, which occurs early and is due to diminished 1-α hydroxylase substrate, mass, and activity (Figure 9-4, Table 9-2).[12–14] 25(OH)D and calcitriol concentrations are directly correlated in CKD, in contrast to persons with normal kidney function, suggesting that calcitriol synthesis may be more substrate-dependent in the setting of CKD.[15–17] Still, diminished 1-α hydroxylase activity is probably the most important cause of

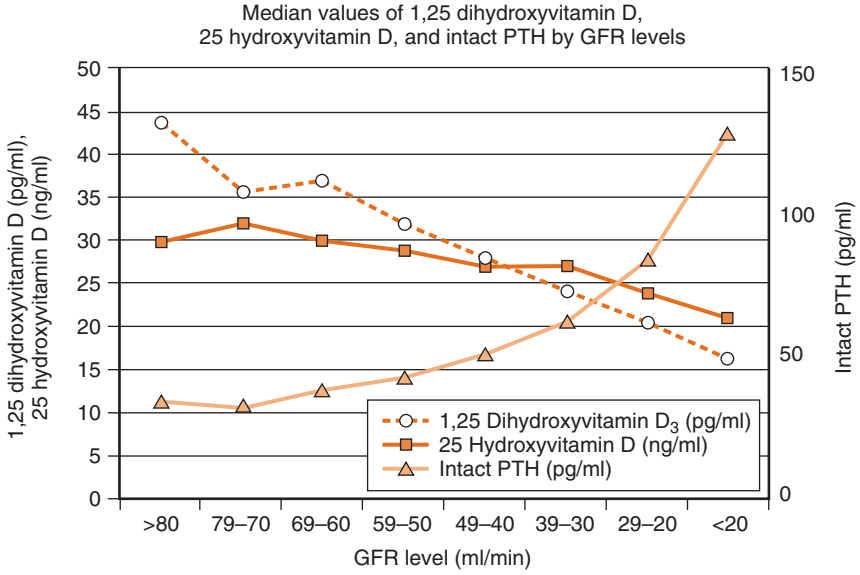


FIGURE 9-4 Median concentrations of serum 25-hydroxyvitamin D, calcitriol, and intact parathyroid hormone by estimated glomerular filtration rate (GFR). (Adapted from A. Levin, G.L. Bakris, M. Molitch, et al., Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease, Kidney Int. 71 [1] [2007] 31-38.)

TABLE 9-2 Causes of Calcitriol Deficiency in CKD
Reduced vitamin D substrate
Decreased cutaneous synthesis
Older age
Non-Caucasian race/ethnicity
Decreased sun exposure
Inefficient synthesis (uremia)
Decreased dietary consumption
Decreased intake of fatty fish
Decreased intake of fortified diary products
Obesity
Urinary losses (proteinuria)
Reduced 1-α hydroxylase mass
Loss of nephrons
Reduced 1-α hydroxylase activity
High FGF-23
Hyperphosphatemia
Diabetes
Metabolic acidosis
Elevated uric acid

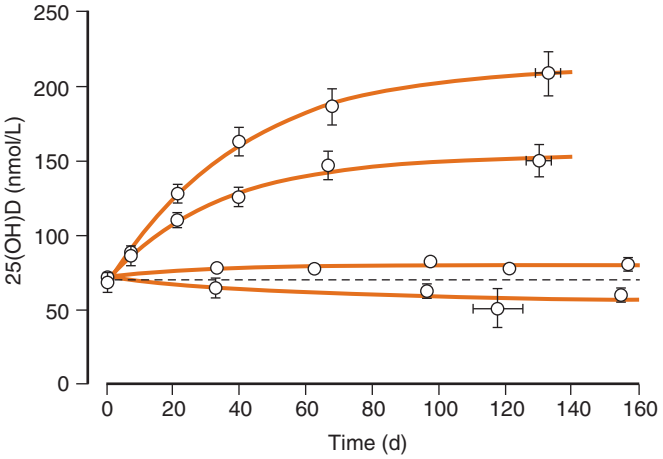


FIGURE 9-5 Changes in serum 25-hydroxyvitamin D concentration in response to graded oral dosing of cholecalciferol during winter months among 67 men living in Omaha, Nebraska. The curves, from the lowest upward, are for 0, 25, 125, and 250 µg cholecalciferol per day (To convert nmol/L to ng/mL, divide by 2.496; to convert µg to international units, multiply by 40). *Points* are mean values, and *error bars* represent 1 SEM. (Adapted from R.P. Heaney, K.M. Davies, T.C. Chen, et al., Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol, Am. J. Clin. Nutr. 77 [1] [2003] 204-210.)

declining calcitriol levels in CKD. Hyperphosphatemia, hyperuricemia, metabolic acidosis, and diabetes are associated with decreased 1-α hydroxylase activity.[8,12,14,18,19] Elevated levels of FGF-23, which acts to maintain serum phosphorous concentration as glomerular filtration rate (GFR) falls, potently suppress 1-α hydroxylase activity.[9,10] This is part of a negative feedback loop, whereby calcitriol stimulates FGF-23 release from osteocytes and osteoblasts, and FGF-23 down-regulates further calcitriol production. Hyperparathyroidism secondary to calcitriol deficiency is a common complication of CKD (see Figure 9-4, see Chapter 8).[20]

EPIDEMIOLOGY

Assessment of Vitamin D Deficiency

Measurement of serum 25(OH)D is the cornerstone of evaluating for vitamin D deficiency. Serum 25(OH)D concentration is widely believed to be a valid gauge of vitamin D status because its concentration reliably increases in a dose-dependent fashion with either cutaneous or oral vitamin D intake (Figure 9-5).[1–3,21–25] Also, the half-life of circulating 25(OH)D is 10 to 21 days, so that a single measurement plausibly reflects intake over the last 2 to 3 months.

25(OH)D circulates at a reasonably high concentration (ng/ml), and a number of assays are available to accurately measure its concentration in serum.[26] Common methodologies include radioimmunoassay and mass spectrometry. Most assays in wide use today detect both 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2. 25-hydroxyvitamin D3 constitutes most or all of the measureable circulating 25(OH)D in the majority of people. Nonetheless, measurement of both forms (total 25 [OH]D) is important, particularly in the setting of ergocalciferol supplementation. When laboratories report 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2 concentrations separately, the total 25(OH)D concentration, not its individual components, is most clinically relevant.

Although serum 25(OH)D concentration is a common and useful laboratory assay, two caveats deserve mention. First, there is currently no accepted standardization for 25 (OH)D, so comparisons of normal or desired ranges from laboratory to laboratory and translation of research to clinical practice can be difficult. Second, although 25(OH)D concentration reliably rises within individuals with vitamin D intake, other factors that influence variation in 25(OH)D concentration between individuals (which may include genetic polymorphisms, liver disease, or other host factors) are not well-understood at this time.

Definition of Vitamin D Deficiency

Low 25(OH)D concentrations are commonly used to evaluate vitamin D status, but thresholds defining vitamin D deficiency are controversial and have changed over time.[27] Older thresholds (< 10 ng/ml, < 12 ng/ml) were based on the statistical distribution of 25(OH)D concentration in the general population. However, defining deficiency by a 2.5th or 5th percentile is arbitrary, and it is now realized that many more people may have inadequate vitamin D. Thus, thresholds based on biological response have been sought.

Several studies have assessed cross-sectional correlations of 25(OH)D concentration with surrogate outcomes thought to respond directly to vitamin D. These outcomes consist of circulating PTH concentration, bone mineral density, and intestinal calcium absorption. In Caucasian populations, serum 25(OH)D and PTH concentrations are inversely correlated below a 25(OH)D threshold of approximately 30 ng/ml (Figure 9-6).[28–30] A similar relationship is seen correlating 25(OH)D concentration with bone mineral density.[31,32] Similarly, intestinal calcium absorption was more efficient among participants with a mean 25(OHD)

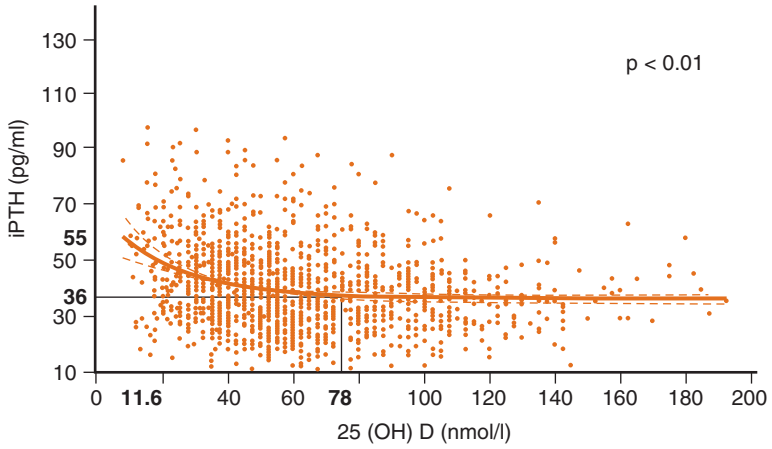


FIGURE 9-6 Cross-sectional association of 25-hydroxyvitamin D and intact parathyroid hormone (iPTH) concentrations among French men and women. The *curved dark line* represents a smoothed mean parathyroid hormone concentration, which begins to rise below a 25-hydroxyvitamin D concentration of approximately 78 nmol/L. To convert nmol/L to ng/mL, divide by 2.496. (Adapted from M.C. Chapuy, P. Preziosi, M. Maamer, et al., Prevalence of vitamin D insufficiency in an adult normal population, Osteoporos. Int. 7 [5] [1997] 439-443.)

of 35 ng/ml, compared to 20 ng/ml.[33] These relationships have been used to define vitamin D insufficiency as a 25(OHD) concentration less than 30 ng/ml and to advocate for interventions maintaining 25(OHD) concentrations above this threshold.[2,27]

One intervention study assessed the question of 25(OH)D threshold.[34] Change in PTH concentration was examined in response to ergocalciferol supplementation, stratified by baseline 25(OH)D concentration. PTH concentration decreased with therapy when baseline 25(OH)D was below 20 ng/ml, but not when baseline 25(OH)D was above 20 ng/ml, suggesting that 20 ng/ml was a threshold concentration needed to maximize this outcome.

Circulating 25(OH)D concentrations vary substantially by race and ethnicity, due to differences in cutaneous synthesis attributable to skin pigmentation, and by season, due to sunlight exposure (see Figure 9-3). Unfortunately, adequate data have not currently been published to determine whether separate thresholds of 25(OH)D should be used to define vitamin D deficiency by race and ethnicity or season.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency is highly prevalent in the general population when it is defined using any common 25(OH) D threshold (Figure 9-7). United States prevalence estimates were generated from data collected as part of the National Health and Nutrition Examination Survey.[35] These estimates vary by age, gender, and race and ethnicity.

Race and ethnicity strongly impact vitamin D metabolism. 25-hydroxyvitamin D concentration varies strongly by race and ethnicity due to differences in skin pigmentation and cutaneous cholecalciferol synthesis, being highest in Caucasian populations, intermediate in Hispanic populations, and lowest in African American populations.[35–37] As would be expected given differences in 25-hydroxyvitamin D, PTH concentrations are highest among African Americans.[38] However, 1,25-dihydroxyvitamin D concentrations are not lower comparing groups of African American versus Caucasian race, suggesting that racial and ethnic differences in vitamin D metabolism are complex and involve differential regulation of key vitamin D-processing enzymes.[39]

In addition, disease-based and lifestyle risk factors for 25(OH)D deficiency are well-described (Table 9-3). The

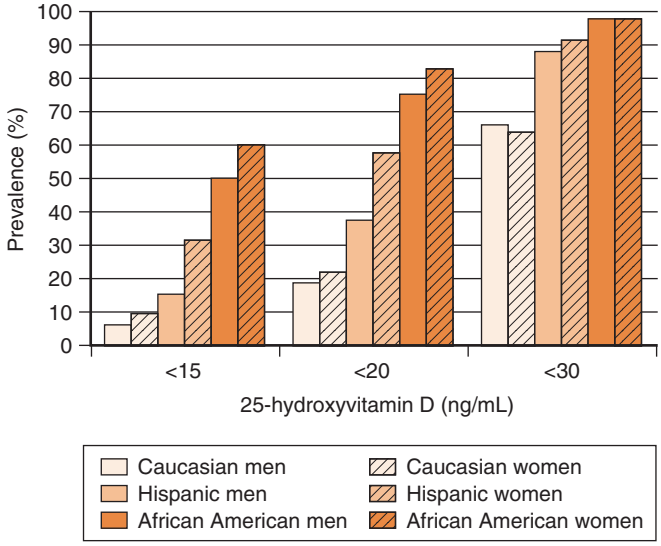


FIGURE 9-7 Prevalence of vitamin D deficiency in the United States population, ages 20 to 49 years, by threshold 25-hydroxyvitamin concentration, gender, and race/ethnicity. (Data from the National Health and Nutrition Examination Survey [2000–2004] are adapted from A.C. Looker, C.M. Pfeiffer, D.A. Lacher, et al., Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004, Am. J. Clin. Nutr. 88 [6] [2008] 1519-1527.)

prevalence of 25(OH)D deficiency in the general population appears to be increasing over time, attributable largely to increasing obesity and sunscreen use and decreased intake of fortified dairy products.[35]

The prevalence of 25(OH)D deficiency in persons with CKD has not been studied using rigorous population-based sampling methods. Nonetheless, most studies suggest that the prevalence of 25(OH)D deficiency in CKD is quite high (Table 9-4).[40,41] Contributing factors may include decreased cutaneous synthesis (due to older age, race and ethnicity, comorbidities, and decreased physical activity); decreased dietary intake of fortified dairy products; obesity; and renal 25(OH)D losses, which are most severe with heavy proteinuria.[42,43] Many of these risk factors (e.g., age, non-Caucasian race/ethnicity, see Table 9-3) are not unique to CKD but are more prevalent in this population, whereas other risk factors (e.g., proteinuria) are specific to patients with CKD.

TABLE 9-3 Risk Factors for 25-Hydroxyvitamin D Deficiency
Reduced sun exposure
Residence in northern latitudes
Indoor occupation
Little outdoor leisure-time physical activity
Reduced rate of cutaneous synthesis
Older age
Non-Caucasian race
Use of sun protective clothing
Use of sunscreen
Reduced dietary intake
Low intake of fatty fish
Low intake of fortified dairy products
Inflammatory bowel disease
Gastric/enteric surgery
Other causes of malabsorption
Increased volume of distribution
Obesity
Renal losses
Nephrotic syndrome

TABLE 9-4 Prevalence of 25-Hydroxyvitamin D Deficiency in CKD		
	THRESHOLD USED TO DEFINE 25-HYDROXYVITAMIN D DEFICIENCY	
CKD STAGE	<15 ng/ml	<30 ng/ml
3 to 4	14% to 44%	71% to 86%
ESRD	14% to 51%	51% to 92%

Calcitriol Deficiency

As the most potent metabolite of vitamin D, calcitriol is a central molecule in mineral metabolism pathophysiology. Nevertheless, measurement of serum calcitriol has limited application in the clinical evaluation of vitamin D deficiency. This is largely because calcitriol has two unfavorable characteristics as a laboratory assay. First, it is present in blood at very low concentrations (pg/ml), and due to difficult isolation and purification, existing assays may also detect other vitamin D metabolites.[44] Second, the half-life of circulating calcitriol is short (approximately 6 hours), so that single measurements may poorly reflect long-term concentrations. Thus, the main clinical use of the serum calcitriol assay is to diagnose cases of hypercalcemia caused by excessive nonrenal calcitriol production (e.g., granulomatous diseases).

Because direct measurement of calcitriol deficiency is difficult, clinical care frequently relies on markers of downstream biological response indicating functional insufficiency of calcitriol. Elevated circulating PTH concentration is the main such marker. Calcitriol and its precursors downregulate PTH by preventing parathyroid hyperplasia and by reducing PTH production and secretion (see Chapter 8).[2,11,45,46] Thus, although elevated serum PTH concentration has a number of implications and consequences, it may in part reflect functional deficiency of vitamin D, and vitamin D therapy is often prescribed in this setting (see Therapy section and Chapter 8).

TABLE 9-5 Locations of the Vitamin D Receptor
Adipose tissue
Bone
Brain
Breast
Cartilage
Colon
Epididymis
Hair follicle
Heart
Intestine
Kidney
Liver
Lung
Lymphocytes
Monocytes/macrophages
Muscle, striated
Neurons
Ovary
Pancreas (β cells)
Parathyroid
Parotid
Pituitary
Placenta
Prostate
Retina
Skin
Stomach
Testis
Thymus
Thyroid
Uterus
Vascular smooth muscle

CONSEQUENCES

Pleiotropy

Vitamin D is long recognized as a key factor maintaining calcium, phosphorous, and bone homeostasis (see Chapter 8).[2,45–47] However, vitamin D receptors are present throughout the body in diverse tissues (Table 9-5), and hundreds of human genes contain vitamin D response elements.[11,48] Thus, pleiotropic actions have been postulated for vitamin D beyond those traditionally described for maintenance of calcium homeostasis and bone health (Figure 9-8). These are described in detail hereafter.

Autocrine and Paracrine Effects

The enzyme 1-α hydroxylase is also expressed outside of the kidney (Table 9-6).[11,48] This observation has led to the suggestion that tissue-specific production of calcitriol may have important autocrine and/or paracrine effects. For example, calcitriol production was demonstrated to be a key autocrine

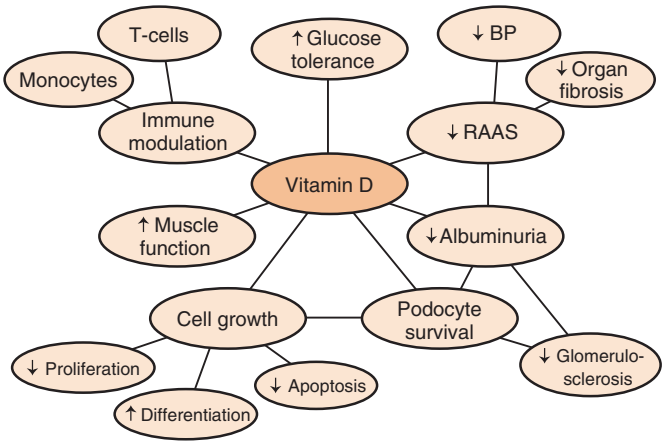


FIGURE 9-8 Potential pleiotropic actions of vitamin D. *BP*, blood pressure; *RAAS*, reninangiotensin-aldosterone system.

TABLE 9–6 Locations of 1-α Hydroxylase

Bone
Brain
Breast
Colon
Dendritic cells
Endothelial cells
Kidney
Monocytes/macrophages
Pancreas (β cells)
Parathyroid
Placenta
Prostate
Skin
Testis
Vascular smooth muscle

mechanism through which tissue macrophages combat tuberculosis.[49] Binding of tuberculosis antigen to the macrophage cell-surface toll-like receptor leads to upregulated expression of the 1-α hydroxylase and vitamin D receptor genes. Calcitriol then induces a cascade of intracellular signaling pathways that culminate in macrophage synthesis of the antimicrobial peptide cathelicidin and killing of intracellular mycobacteria. Sera from African American individuals with low circulating 25-hydroxyvitamin D concentrations were inefficient in supporting cathelicidin messenger RNA induction, offering a potential explanation for the increased susceptibility to tuberculosis observed in African Americans. Intriguingly, the dependence of macrophage activity on 25(OH)D may have led to improved tuberculosis outcomes when patients were historically moved to tuberculosis sanitaria in sunny locations.

It is important to note that nonrenal 1-α hydroxylase activity is likely to be regulated differently than renal 1-α hydroxylase activity. In addition, the relative contribution of calcitriol produced at the systemic level (kidney) versus tissue level (local) remains to be determined for most potential pleiotropic effects of vitamin D.

Mortality

Patients with CKD have a markedly increased mortality rate, due in large part to increased risk for cardiovascular disease (CVD).[50,51] Vitamin D deficiency may contribute to poor clinical outcomes. Recently, low circulating 25(OH)D and calcitriol concentrations were associated with increased risks of mortality among incident hemodialysis patients and patients with stage 2 to stage 5 CKD.[17,41] Low circulating 25(OH)D concentrations were also associated with adverse health outcomes among populations with predominantly normal kidney function: cardiovascular events in the Framingham Offspring Study, myocardial infarction in the Health Professionals Follow-up Study, cardiovascular- and all-cause mortality among patients with acute coronary syndrome, and all-cause mortality in follow-up from the Third National Health and Nutrition Examination Survey (NHANES III).[52–55]

A number of observational cohort studies have reported that treatment with calcitriol or an activated vitamin D analogue is associated with decreased risk for mortality and/or CVD events in CKD (Figure 9-9).[56–62] Combined, these studies suggest that therapy with calcitriol or an analog is associated with an approximately 20% reduction in risk of death in patients with CKD. Importantly, these studies also observed 1) that the beneficial effect of calcitriol does not depend on baseline PTH concentration, suggesting that using PTH alone as an indication for therapy may not optimally

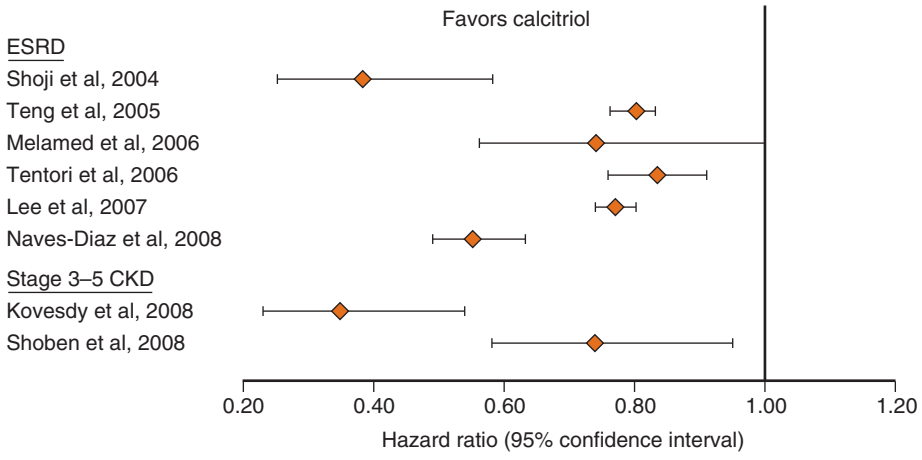


FIGURE 9-9 Associations of therapy with calcitriol or an analogue with mortality among persons with chronic kidney disease. *Diamonds* represent hazard ratio point estimates, *horizontal bars* represent 95% confidence intervals.

identify persons who may benefit from calcitriol therapy; and 2) no clear dose-response of association of calcitriol with mortality, suggesting that lower doses of calcitriol may be as beneficial as higher doses. However, observational studies of medications have an important limitation—the potential for confounding by indication.[63] Thus, randomized clinical trials are needed to test the hypothesis that vitamin D therapy improves clinical outcomes in patients with CKD.

Cell Growth and Differentiation

Vitamin D is known to affect cell proliferation, differentiation, and survival. In general, vitamin D promotes cell differentiation, reduces cell proliferation, and has complex actions to modulate apoptosis.[64–68] These actions are mediated in part through regulation of cell cycle progression, with effects on the cyclins, cyclin-dependent kinases, and cyclin kinase inhibitors that govern cell cycle transitions. Due to these and other observations, it has been hypothesized that vitamin D helps to prevent a number of cancers, particularly prostate, breast, and colon cancers.[69–72] Data regarding the anticancer effects of vitamin D are not conclusive at this time. Vitamin D may also have important effects on the growth and differentiation of nonmalignant cells (see *Immune Cell Function, Glucose Metabolism, Cardiovascular Disease,* and *Chronic Kidney Disease* hereafter).

Immune Cell Function

In vitro cell culture studies and *in vivo* animal-experimental models demonstrate potent immunomodulatory functions of vitamin D metabolites.[73] In general, vitamin D tends to enhance innate immunity and suppress cellular immunity. Effects on innate immunity include enhanced activity of tissue macrophages, as described previously for tuberculosis (see Autocrine and Paracrine Effects). Regarding cellular immunity, both antigen presenting cells and T-cells are affected. In antigen presenting cells, including monocytes, calcitriol alters cytokine expression (decreased interleukin-1, interleukin-6, interleukin-8, interleukin-12, and tumor necrosis factor-α; increased interleukin-10) and regulates cell growth and cell-cell interaction. These effects decrease cell differentiation, maturation, major histocompatibility complex–II expression, costimulatory molecule expression, and interferon-γ expression, and increase apoptosis.[74–77] Downstream, development and activation of T-cells is suppressed. Vitamin D also has direct effects on T-cells, including inhibition of autocrine IL-2 production. Thus, the net result of vitamin D on cellular immunity includes inhibition of antigen presentation, decreased T-cell proliferation, and a shift in the composition of T-cell subpopulations.

Given these effects of vitamin D on immune cell function, vitamin D deficiency has been hypothesized to contribute to a number of autoimmune diseases. Specifically, existing evidence suggests that vitamin D insufficiency may contribute to the pathogenesis of multiple sclerosis, type I diabetes, and Crohn disease.[78–80] Vitamin D deficiency may play a role in the systemic inflammation observed in CKD, and vitamin D may have relevant effects on immune tolerance and rejection after kidney transplantation.

Renin-Angiotensin-Aldosterone System

Li and colleagues demonstrated that calcitriol is a potent suppressor of renin production in the mouse kidney.[81] Renin mRNA and protein levels were markedly elevated in vitamin D receptor null mice, which as a result had elevated levels of circulating angiotensin II and blood pressure. Results were confirmed using wild type mice induced to dietary vitamin D deficiency, whose elevated renin levels were rescued by calcitriol therapy. Cell culture models showed that that calcitriol reduced renin transcription via promoter downregulation. Subsequently, renal production of renin, and other components of the renin-angiotensin-aldosterone system (RAAS), was observed to be reduced in a variety of animal models. In humans, circulating calcitriol concentrations are inversely correlated with blood pressure, and lower 25(OH) D concentrations are associated with increased risk of developing hypertension.[82–85]

Glucose Metabolism

Glucose metabolism is frequently impaired in CKD.[86] In end-stage renal disease (ESRD), the most profound disturbance is insulin resistance due to a post receptor defect in skeletal muscle.[87,88] Some ESRD patients are able to compensate for insulin resistance by increasing insulin secretion, but defects in insulin secretion are also common.[87,89] These abnormalities result in glucose intolerance. Insulin resistance appears to be common in earlier stages of CKD as well,[40,90] though evaluation has been limited by the confounding effect of renal insulin clearance and by a lack of studies using gold standard measurements.

Vitamin D may improve glucose metabolism by stimulating insulin secretion from pancreatic beta cells and by improving peripheral insulin sensitivity. In seminal work by Norman and colleagues, administration of cholecalciferol to vitamin D-deficient rats more than doubled insulin secretion from isolated perfused pancreas.[91] Subsequent studies have suggested that the mechanism for this effect is increased insulin release through stimulation of intracellular free calcium.[92] Modulation of the immune system has been proposed as an additional mechanism through which vitamin D may preserve long-term beta cell function (and prevent type I diabetes), and vitamin D could potentially protect beta cells through effects on cell proliferation, differentiation, and apoptosis.[11,73] Vitamin D may also affect insulin sensitivity through actions on the insulin receptor. A vitamin D response element has been described in the promoter region of the human insulin receptor gene, and calcitriol stimulated insulin receptor expression and insulin responsiveness for glucose transplant in cultured human promonocytic cells.[93–95]

Intervention studies have consistently shown benefits of calcitriol therapy on glucose metabolism in the setting of maintenance hemodialysis (Table 9-7).[96–104] Each of these studies employed before-treatment and after-treatment comparisons to demonstrate improvement of insulin secretion, insulin action, and/or glucose tolerance after a relatively short duration of calcitriol therapy (Figure 9-10, for example). In studies that included a comparison group without kidney disease, measures of glucose metabolism were

TABLE 9-7 Intervention Studies Assessing the Effects of Calcitriol on Glucose Metabolism Among Hemodialysis Patients

FIRST AUTHOR (YEAR)	N	CALCITRIOL DOSE	DURATION	OUTCOME (METHOD OF ASCERTAINMENT)
Quesada (1990)[99]	9	0.5 μg/d	2 weeks	↑ insulin secretion (OGTT)
Mak (1992)[96]	11	2 μg/m^2	Single dose	↑ glucose tolerance (IVGTT), ↑ insulin secretion (hyperglycemic clamp)
Mak (1992)[97]	7	2 μg/m^2	Single dose	↑ insulin sensitivity (hyperglycemic clamp)
Allegra (1994)[100]	17	0.5 μg/d	3 weeks	↑ insulin secretion (IVGTT)
Lin (1994)[101]	15	2 μg thrice weekly	8 weeks	↑ glucose tolerance, ↑ insulin secretion (OGTT)
Kautzky-Willer (1995)[102]	10	Mean 1 μg thrice weekly*	12 weeks	↑ insulin sensitivity (frequently sampled IVGTT)
Mak (1998)[98]	8	1.5–2.5 μg thrice weekly*	4 weeks	↑ glucose tolerance (OGTT), ↑ insulin sensitivity (euglycemic clamp)
Khajehdehi (2003)[103]	48	0.030 μg/kg twice weekly	3 months	↓ fasting glucose
Strozecki (2004)[104]	8	1–2 μg thrice weekly*	12 weeks	↓ hemoglobin A1c, no change in fasting glucose or insulin

*Titrated dose.
IVGTT, intravenous glucose tolerance test; *OGTT*, oral glucose tolerance test.

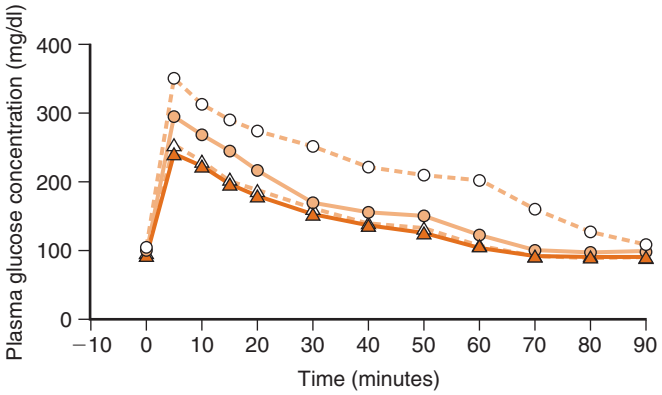


FIGURE 9-10 Plasma glucose concentrations after an intravenous glucose bolus. Results are shown for 11 hemodialysis patients before (○) and after (●) a single intravenous dose of calcitriol (2 μg/m^2), and for 11 healthy control subjects before (Δ) and after (▲) the same calcitriol intervention. Glucose intolerance in hemodialysis patients is observed as higher glucose concentrations following glucose challenge, compared to healthy controls. This difference is substantially attenuated with calcitriol therapy. (Adapted from R.H. Mak, Intravenous 1,25 dihydroxycholecalciferol corrects glucose intolerance in hemodialysis patients, Kidney Int. 41 [4] [1992] 1049-1054.)

substantially worse among hemodialysis patients and returned to normal or near-normal with calcitriol.[96-98,100–102,104] Effects of vitamin D products on glucose metabolism among people with normal kidney function have been mixed and generally less impressive.[86,105,106]

Cardiovascular Disease

CVD is the most common cause of death among people with CKD.[107] Thus, if vitamin D therapy improves survival in CKD (see *Mortality*), it is likely to have a beneficial effect on CVD. There are a number of mechanisms through which vitamin D may help prevent CVD (Figure 9-11). As one of its effects on immune cell function, vitamin D influences the development of T-cell subsets, promoting the generation of regulatory T-helper type 2 (Th2) lymphocytes over proatherogenic Th1 lymphocytes.[108] Through these immunological effects, and the effects on glucose metabolism and the RAAS system discussed previously, vitamin D may help prevent the development of atherosclerosis.

Vitamin D may also have direct effects on vascular smooth muscle cells. Specifically, calcitriol may modulate expression of genes that regulate transformation of vascular smooth muscle cells to an osteoblast-type phenotype.[14,108] In animal models, doses of calcitriol sufficient to suppress PTH reduce vascular calcification, whereas higher doses stimulate vascular calcification, possibly due in part to resultant hyperphosphatemia and hypercalcemia.[109] In humans, low 25(OH)D concentrations have been associated with increased risks of developing coronary artery calcification, and circulating calcitriol concentrations have been reported to correlate inversely with coronary artery calcification.[110,111]

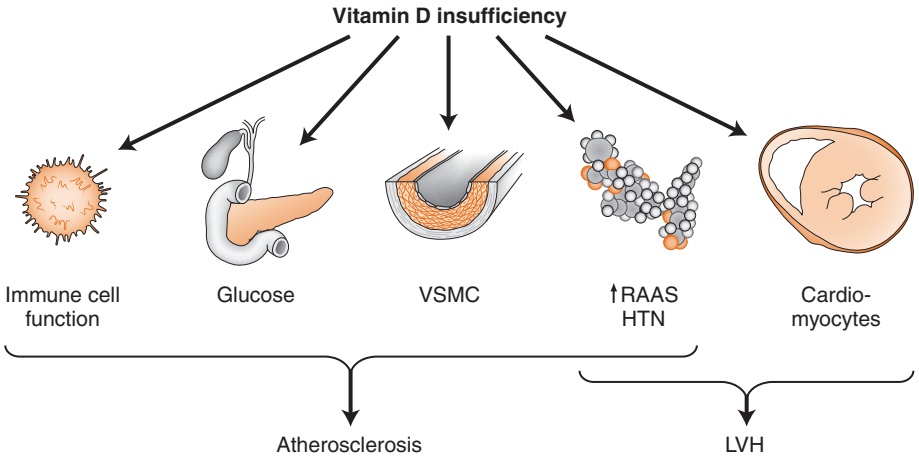


FIGURE 9-11 Mechanisms through which vitamin D may help prevent cardiovascular disease. *LVH*, left ventricular hypertrophy; *RAAS*, renin-angiotensin-aldosterone system; *VSMC*, vascular smooth muscle cells.

In addition, vitamin D may help prevent left ventricular hypertrophy (LVH). Animal models demonstrate that vitamin D deficiency promotes LVH through direct and indirect effects on cardiomyocytes. Rodents with dietary vitamin D deficiency or targeted deletion of the vitamin D receptor or 1-α hydroxylase develop a phenotype of hypertension, cardiomyocyte hypertrophy, and left ventricular enlargement, whereas treatment with 1,25-dihydroxyvitamin D prevents this phenotype.[112–115] In these models, adverse effects of vitamin D deficiency are mediated by activation of the cardiac and systemic RAAS and by direct effects promoting cell growth.[113–116] In humans, LVH leads to coronary ischemia, congestive heart failure, cardiac arrhythmias, and death. In patients with ESRD, low 25(OH)D concentrations have been associated with vascular stiffness.[117] Thus, LVH may represent a causal intermediary between vitamin D deficiency and cardiovascular mortality.

Chronic Kidney Disease

Vitamin D may help prevent kidney disease through a number of mechanisms (Figure 9-12). First, suppression of the RAAS may prevent kidney damage by reducing both blood pressure (systemic effect) and transforming growth factor β–mediated fibrosis (local effect).[118] Second, vitamin D has direct effects on podocyte proliferation and differentiation that appear to prevent apoptosis and cell death. Third, salutary effects on inflammation and glucose metabolism may improve the metabolic milieu of the kidney.

Potent beneficial effects of calcitriol have been observed in animal models of CKD. In five-sixth nephrectomy (remnant kidney) and streptozotocin (type 1 diabetes) models, calcitriol or its analogues reduce local levels of RAAS components, albuminuria, and glomerulosclerosis.[119] These salutary effects appear to be more pronounced with concurrent RAAS inhibitor therapy, which is known to otherwise cause a compensatory increase in renal renin production.[120]

In the United States population, low 25(OH)D concentrations are associated with increased risk of albuminuria (Figure 9-13).[36] Two randomized clinical trials of paricalcitol in stages 3 and 4 CKD have evaluated change in albuminuria as a secondary outcome. Among 118 participants with dipstick albuminuria at baseline, albuminuria regressed in 29 of 57 participants assigned to active treatment for 24 weeks (51%), compared to 25% of participants assigned to placebo ($p = 0.004$).[121] In a 24-person, 1-month trial, albuminuria was reduced by almost 50% among participants assigned to active therapy, compared to an increase of more than 30% for participants assigned to placebo ($p = 0.0005$).[122] Some observational studies suggest that calcitriol therapy may prevent progression of CKD, though this observation is not consistent.[56,60] No clinical trials of vitamin D, calcitriol, or its analogues have tested whether vitamin D improves long-term renal outcomes.

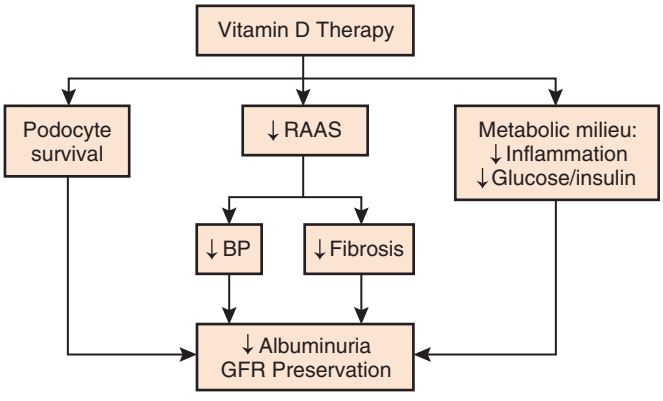


FIGURE 9-12 Mechanisms through which vitamin D may help prevent chronic kidney disease and its progression. *BP*, blood pressure; *GFR*, glomerular filtration rate; *RAAS*, renin-angiotensinaldosterone system.

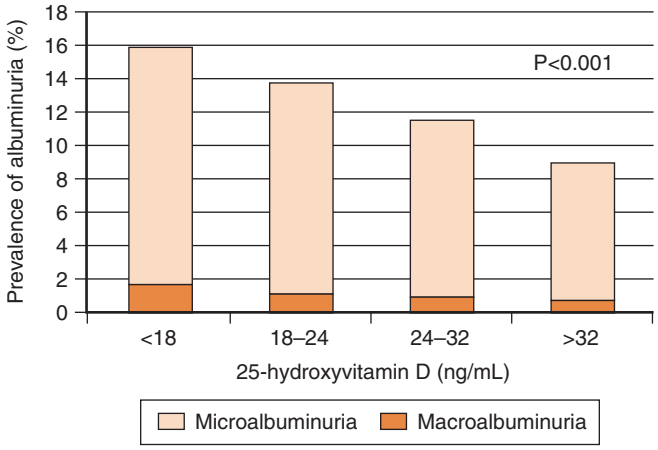


FIGURE 9-13 Association of 25-hydroxyvitamin D concentration with prevalent albuminuria in the United States population. Micro- and macroalbuminuria are defined using gender-specific thresholds of urine albumin-creatinine ratio. (Adapted from I.H. de Boer, G.N. Ioannou, B. Kestenbaum, et al., 25-Hydroxyvitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey [NHANES III], Am. J. Kidney Dis. 50 [1] [2007] 69-77.)

THERAPY

Goals of Therapy

A fundamental challenge in the treatment of vitamin D deficiency is establishing appropriate goals of therapy. As discussed previously, there are many potential pleiotropic actions of vitamin D that may lead to improved patient outcomes. Unfortunately, there are currently no clinical assays available to directly gauge the effect of vitamin D on these pleiotropic pathways. Moreover, several studies suggest that salutary effects of calcitriol therapy do not depend on pretreatment levels of PTH, the traditional measurement used to titrate vitamin D interventions in the setting of CKD. As a result, some experts have suggested that all CKD patients receive vitamin D treatment, regardless of laboratory parameters. More commonly, however, clinicians target vitamin D therapy to one or two laboratory parameters: 25(OH)D and/or PTH. In theory, repletion of 25(OH)D is a relatively safe intervention that maximizes potential autocrine and/or paracrine effects of vitamin D, and titration to PTH maximizes bone health and offers a potential "readout" of vitamin D functional status.

Current Practice by Stage of Chronic Kidney Disease

Current approaches to vitamin D therapy vary by the presence and severity of kidney disease. In the general population, renal 1-α hydroxylase activity is generally preserved. "Vitamin D status" is ascertained by 25(OH)D concentration, and forms of vitamin D that required activation by 1-α hydroxylase (cholecalciferol or ergocalciferol) are administered orally. In dialysis patients, 1-α hydroxylase activity is markedly diminished. Vitamin D therapy is usually based on circulating PTH concentration, and therapy is administered as calcitriol or its analogues, often intravenously. In earlier stages of CKD, approaches to evaluation and treatment are heterogeneous. These involve titration to 25(OH)D and/or PTH and use of the full spectrum of vitamin D therapies. After kidney transplantation, bone loss is a major consideration, and calcitriol is commonly prescribed in combination with calcium salts.

Cholecalciferol

Cholecalciferol therapy offers numerous advantages for the treatment of vitamin D deficiency (Table 9-8). It is the best-studied form of vitamin D, and the only form that has been studied for long periods of follow-up in controlled settings. Doses up to 10,000 international units daily have been studied for up to 6 months duration, and doses up to 800 international units daily have been studied for many years duration. In clinical trials, increasing doses of cholecalciferol result in reliable dose-dependent increases in 25(OH)D concentrations (see Figure 9-2).[25] On average, each 1000 international units/day raises 25(OH)D by 6 to 10 ng/ml (Figure 9-14).[24,25] Repletion of 25(OH)D should facilitate any autocrine/paracrine actions of vitamin D. Moreover, cholecalciferol has been proven in randomized trials to improve some clinical outcomes; when administered with calcium in the setting of osteoporosis, cholecalciferol prevents fractures. Cholecalciferol is also inexpensive. Because of the long half-life of circulating 25(OH)D, cholecalciferol can be administered weekly, and it has been evaluated in monthly dosing.

Fewer adverse effects are observed with cholecalciferol therapy, compared with calcitriol therapy, because regulation by 1-α hydroxylase helps prevent excess calcitriol production. Few short-term adverse effects have been reported with cholecalciferol, including administration at very high doses, but long-term therapy does increase the risk of kidney stones when administered with calcium. In the Women's Health Initiative Calcium-Vitamin D trial, administration of calcium plus cholecalciferol (1000 mg plus 400 international units daily, respectively) increased the 7-year cumulative incidence of kidney stones from 2.1% to 2.5% ($p < 0.05$). This is presumably due to modest chronic increases in dietary calcium absorption with resultant increased urinary calcium excretion.

Among persons with CKD, both before and after the initiation of dialysis, cholecalciferol supplementation has been evaluated in a small number of observational studies and clinical trials.[123–126] To date, each of these is a relatively small, single-center study, and many were not controlled. Over 1 month to 2 years follow-up,

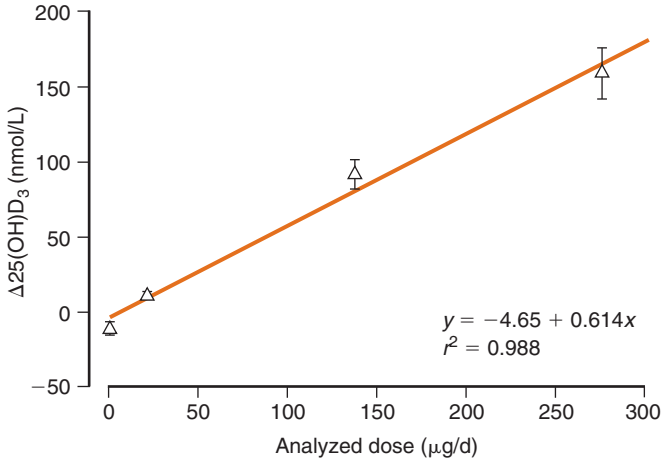


FIGURE 9-14 Relationship between oral cholecalciferol dose (*x axis*) and change in circulating 25-hydroxyvitamin D concentration (*y axis*) after 5 months of treatment during winter months for 67 men living in Omaha, Nebraska. (To convert nmol/L to ng/mL, divide by 2.496; to convert μg to IU, multiply by 40.) (Reproduced from R.P. Heaney, K.M. Davies, T.C. Chen, et al., Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol, Am. J. Clin. Nutr. 77 [1] [2003] 204-210, with permission.)

TABLE 9-8 Options for Vitamin D Therapy in CKD

THERAPY	ADVANTAGES/DISADVANTAGES
Cholecalciferol	Best-studied form of vitamin D Reliable dose-response Proven to prevent fractures* May facilitate autocrine/paracrine effects of vitamin D Can be administered daily or weekly Inexpensive Safety: regulated conversion by 1-α hydroxylase Few short-term adverse effects Hypercalciuria and kidney stones May not adequately increase systemic calcitriol levels May not adequately suppress PTH
Ergocalciferol	Available in high-dose capsules Can be administered weekly or monthly May facilitate autocrine/paracrine effects of vitamin D Safety: regulated conversion by 1-α hydroxylase May not adequately increase systemic calcitriol levels May not adequately suppress PTH
Calcitriol	Does not require renal activation Known to effectively suppress PTH Associated with improved survival in observational studies Can be administered intravenously with hemodialysis Hypercalcemia and hyperphosphatemia Overtreatment can lead to adynamic bone disease
Other vitamin D receptor agonists	Do not require renal activation Known to effectively suppress PTH Associated with improved survival in observational studies Can be administered intravenously with hemodialysis Less hypercalcemia and hyperphosphatemia than calcitriol Overtreatment can lead to adynamic bone disease

*In the setting of osteoporosis or secondary prevention

cholecalciferol was generally found to effectively raise 25(OH)D concentrations. In pre-ESRD CKD, cholecalciferol tended to reduce PTH concentration by approximately 10%. Few studies evaluated effects on urinary calcium and phosphorous excretion in pre-ESRD CKD, and whether these potentially harmful effects are present or severe is not well-defined. No study reported effects on nontraditional vitamin D outcomes. The main disadvantage of cholecalciferol therapy in CKD is that it may not restore sufficient circulating calcitriol for important endocrine effects, due to impaired renal 1-α hydroxylase activity. In addition, cholecalciferol alone may not suppress PTH concentrations to recommended targets among persons with established parathyroid hyperplasia. Finally, it is possible that any form of vitamin D therapy may facilitate vascular calcification by increasing dietary calcium absorption. The clinical relevance of this potential adverse effect is not currently clear.

Ergocalciferol

Ergocalciferol therapy offers many of the same potential advantages as cholecalciferol, including facilitation of autocrine and paracrine effects and relative safety (see Table 9-8). Compared with cholecalciferol, ergocalciferol is formulated in capsules of larger dose (50,000 international units). This allows less frequent administration, which may lower cost and improve patient adherence. However, many experts cite disadvantages of ergocalciferol. Compared to cholecalciferol, ergocalciferol is less effective at raising 25(OH)D concentrations (international units per international units) and its metabolites may be less potent. This may be due to a relatively greater rate of inactivation (including 24-hydroxylation), which is consistent with an observed shorter half-life for 25(OH)D2 compared with 25(OH)D3. In addition, ergocalciferol has not been shown to prevent fractures.

Published evaluation of ergocalciferol in CKD is similar to evaluation of cholecalciferol.[127–129] It does raise 25(OH)D concentration and tends to modestly suppress PTH. Other potential disadvantages, including hypercalciuria, stones, and ineffective conversion to calcitriol, are similar to cholecalciferol.

Calcitriol

Calcitriol is commonly prescribed and relatively well-studied in the setting of CKD. It does not require renal activation for potent binding to the vitamin D receptor. As a result, it is an established therapy for the treatment of secondary hyperparathyroidism in all stages of CKD and is known to effectively lower serum PTH concentration (see Chapter 8). In addition, calcitriol has been associated with improved survival in observational studies of CKD and ESRD (see **Consequences**). Calcitriol can be administered intravenously with hemodialysis or orally at any stage of CKD.

Because calcitriol potently activates the vitamin D receptor, one potential adverse effect is adynamic bone disease due to oversuppression of PTH (see Chapter 8). In addition, calcitriol carries a risk of hypercalcemia and, less frequently, hyperphosphatemia. Regular monitoring is therefore required.

Other Vitamin D Receptor Agonists

A number of novel vitamin D analogues have been developed. These analogues of calcitriol include paricalcitol and Hectorol, which are available for use in the United States. Vitamin D analogues have differential vitamin D receptor-mediated effects in different tissues and were selected for their ability to reduce circulating PTH concentration while minimizing hypercalcemia, presumably due to a greater ratio of activity in the parathyroid gland versus small bowel. Clinical trials have demonstrated that paricalcitol and Hectorol lower circulating PTH concentrations at least as effectively as calcitriol, with a reduced incidence of hypercalcemia.[130] Relative effects on other tissues, including those that may mediate pleiotropic effects of vitamin D, are not well-described. However, one observational study in a large hemodialysis population suggested that paricalcitol use was associated with better survival than calcitriol use.

Recommendations for Therapy

Currently, there is insufficient high-quality evidence from outcomes-oriented randomized clinical trials to confidently define an ideal approach to vitamin D therapy in CKD. Nonetheless, clinicians and patients must make therapeutic decisions based on available data. These decisions should take into account emerging observations that vitamin D therapy may have clinically relevant pleiotropic actions, that some of these actions may be mediated by nonrenal 1-α hydroxylase, and that many patients with CKD are deficient in both 25(OH)D and calcitriol. Therefore, one approach is to titrate vitamin D therapy to both 25(OH)D and PTH concentration. With this strategy, 25(OH)D concentrations are routinely measured at any stage of CKD, with low levels replenished using cholecalciferol or ergocalciferol. Simultaneously, intact PTH concentrations are measured as an indicator of functional calcitriol status, with calcitriol and its analogues prescribed to lower PTH as needed. When limited by hypercalcemia, or when no longer effective, calcimimetics and surgical parathyroidectomy can be employed to control PTH (see Chapter 8).

UNANSWERED QUESTIONS

There are many unanswered questions in the study of vitamin D deficiency in CKD. Several are particularly pressing. In particular, which potential pleiotropic actions of vitamin D are clinically relevant? How do we gauge whether and how much vitamin D is needed to impact relevant targets? In what form or combinations should we provide vitamin D to affect nontraditional actions? These questions require further studies, with focus on intervention studies in CKD with both short-term surrogate outcomes and long-term clinical outcomes.

CONCLUSION

Vitamin D deficiency is common in patients with CKD. Low 25(OH)D concentrations reflect inadequate intake of cholecalciferol and ergocalciferol from cutaneous synthesis and dietary intake, and low calcitriol levels reflect decreased metabolism of vitamin D to its active hormonal form. Increasing evidence suggests that vitamin D deficiency may have broad-ranging, clinically relevant effects beyond those described for calcium and bone homeostasis. Treatment of vitamin D deficiency in CKD is currently guided by measurement of circulating 25(OH)D and PTH concentrations. A number of therapeutic options are available, and there may be benefit to simultaneous treatment with more than one form of vitamin D.

ACKNOWLEDGMENTS

This publication was made possible by Grant Number 5KL2RR025015-02 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

A full list of references are available at www.expertconsult.com.

Chapter 10

CARDIOVASCULAR DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Daniel E. Weiner, M.D., M.S. and Mark J. Sarnak, M.D., M.S.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). The increased risk of cardiovascular disease begins during the earlier stages of CKD before the onset of kidney failure. Although patients with CKD have a very high prevalence of traditional cardiovascular disease risk factors such as diabetes and hypertension, they are also exposed to other nontraditional, uremia-related cardiovascular disease risk factors such as abnormal calcium-phosphorus metabolism and inflammation. Although some of the burden of cardiovascular disease in CKD may be due to atherosclerosis, it is apparent that patients with CKD also have a high prevalence of arteriosclerosis and disorders of left ventricular structure and function.

In this chapter, we discuss the epidemiology and pathophysiology of CVD in patients with CKD, with a focus on dialysis patients and nontransplant recipients with stages 3 to 4 CKD. We also discuss the different manifestations of CVD in kidney disease and review diagnostic and therapeutic options.

EPIDEMIOLOGY

Dialysis

Among dialysis patients, CVD is the single leading cause of mortality, accounting for nearly 45% of deaths at all ages.[1] The majority of cardiovascular events, approximately 25% to 30% of all deaths (58% to 66% of cardiovascular deaths), are classified as either cardiac arrest or arrhythmia. This high burden of CVD mortality is well-illustrated by comparing CVD mortality in the dialysis population to the general population; at all ages in both men and women, mortality due to CVD is 5 to 45 times higher in dialysis patients who are 45 years old and older and 180 times higher in dialysis patients between the ages of 20 and 45 (Figure 10-1).[1,2]

In theory, the high CVD mortality rate in dialysis patients may be due to both a high prevalence of CVD and a high case fatality rate. In fact, both are true. Based on data obtained from medical evidence forms completed at the time of initiation of kidney replacement therapy, 22.1% of

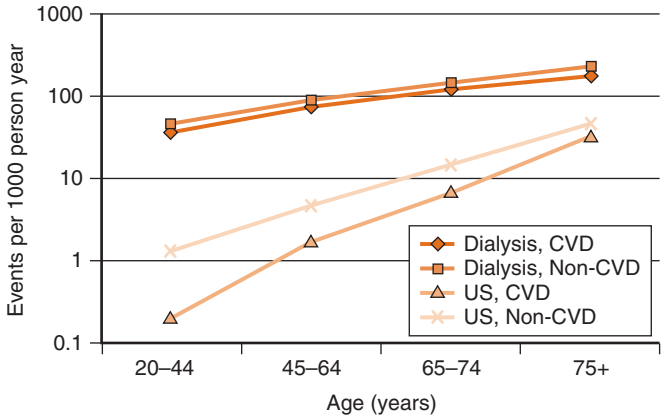


FIGURE 10-1 Cardiovascular and all-cause mortality in the general population and dialysis population. Data on dialysis patients were derived from the USRDS 2008 Annual Data Report and reflect events occurring between 2001 and 2006, whereas data on the general population were derived from the 2008 National Vital Statistics Reports using 2005 data.[1,2] CVD mortality includes death due to myocardial infarction, pericarditis, atherosclerotic coronary disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, congestive heart failure, and cerebrovascular diseases in dialysis patients and is defined by ICD-10 codes I00-I78 in the general population. The youngest age group in the general population is 25 to 44 years old versus 20 to 44 in dialysis.

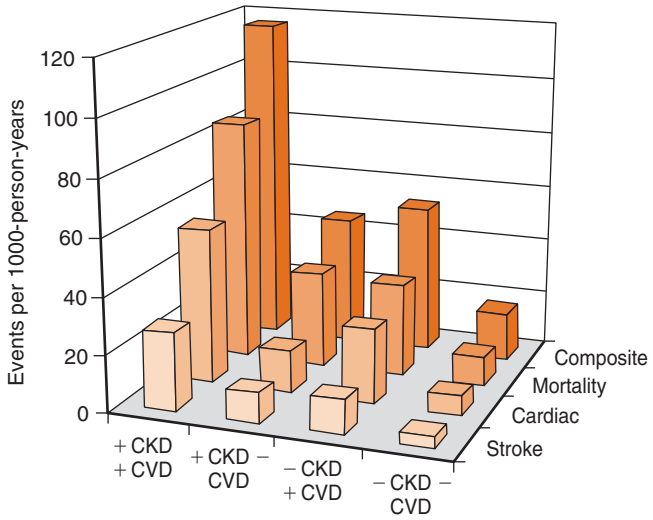


FIGURE 10-2 Event rates for individuals with and without chronic kidney disease (CKD) and cardiovascular disease (CVD). Cardiac events include myocardial infarction and fatal coronary disease. Stroke includes both fatal and nonfatal stroke events. Mortality includes all causes of death, and the composite outcome includes any cardiac, stroke, or mortality event. (Adapted from D.E. Weiner, S. Tabatabai, H. Tighiouart, et al., Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease, Am. J. Kidney Dis. 48 [3] [2006] 392-401.)

patients have known atherosclerotic heart disease, 33.2% have heart failure, 14.7% have peripheral vascular disease, and 9.7% have had strokes or transient ischemic attacks.[1] The prevalence of CVD at initiation of dialysis is even higher if claims data are used instead of the Medical Evidence Form. Dialysis patients with CVD also have a very high case fatality rate. Herzog and colleagues retrospectively studied outcomes of 34,189 dialysis patients and noted a 60% 1-year mortality and 90% 5-year mortality rate following acute myocardial infarction (AMI).[3] Furthermore, in-hospital death among dialysis patients with hospitalization for AMI is nearly twice as frequent as it is among nondialysis patients (21.3% versus 11.7%).[4]

Stage 3 to 4 Chronic Kidney Disease

CVD is highly prevalent in all stages of CKD, with the high prevalence of CVD in incident dialysis patients, suggesting that CVD develops prior to the onset of kidney failure. Several studies have shown that manifestations of CVD, including left ventricular hypertrophy (LVH), may be seen relatively early in CKD.[5] The 2008 USRDS Annual Data Report extended observations to the nondialysis population by including Medicare patients and members of two large health plans and explored the association between earlier stages of CKD and CVD in these populations.[6] Those with CKD, defined by claims data, had three times greater hospitalization rates for AMI stroke and arrhythmia than had those without CKD. Other studies have also demonstrated a higher prevalence of coronary artery disease, heart failure, and CVD risk factors among individuals with CKD.[7–10] For example, among patients with CKD in the Cardiovascular Health Study (CHS, comprised of subjects aged 65 years and older), 26% had coronary artery disease, 8% had heart failure, and 55% had hypertension at baseline, whereas in those without CKD 13% had coronary artery disease, 3% had heart failure, and 36% had hypertension.[11] Similar findings were noted in the Atherosclerosis Risk in Communities (ARIC) study, a community-based cohort of individuals aged 45 to 64 years, wherein participants with estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73m^2 had a baseline prevalence of coronary artery disease, cerebrovascular disease, and diabetes of 11%, 10%, and 24%, respectively, whereas participants without CKD had a baseline prevalence of coronary artery disease, cerebrovascular disease, and diabetes of 4.1%, 4.4%, and 13%, respectively.[12]

Incident CVD is associated with reduced GFR in most but not all cohort studies that have evaluated this relationship (Figure 10-2).[13–16] This association has been particularly strong in populations that include African Americans and in populations evaluating higher risk patients.[13,17–19] For example, in the Studies of Left Ventricular Dysfunction (SOLVD) trial, which included subjects with left ventricular ejection fraction below 35%, and participants with CKD had a 40% increased risk of mortality and a 50% to 70% increased risk of death due to heart failure.[20] Similarly, in the Heart Outcomes and Prevention Evaluation (HOPE) trial, patients with CKD had a 40% increased risk of the composite outcome of myocardial infarction, CVD death, and stroke.[21] The largest population study to date evaluated Kaiser Permanente patients in northern California who had serum creatinine measured as a part of their clinical care and noted a strong, graded relationship between eGFR and subsequent cardiovascular disease outcomes; this was particularly notable below an eGFR of 45 ml/min/1.73 m^2 (Figure 10-3).[22] Similarly, a metaanalysis of 39 community-based studies that included 1,371,990 participants demonstrated increased risk of all-cause mortality associated with eGFR below 60 ml/min/1.73 m^2 in 71% of these cohorts.[23] Accordingly, the presence of reduced GFR likely identifies a high-risk population.

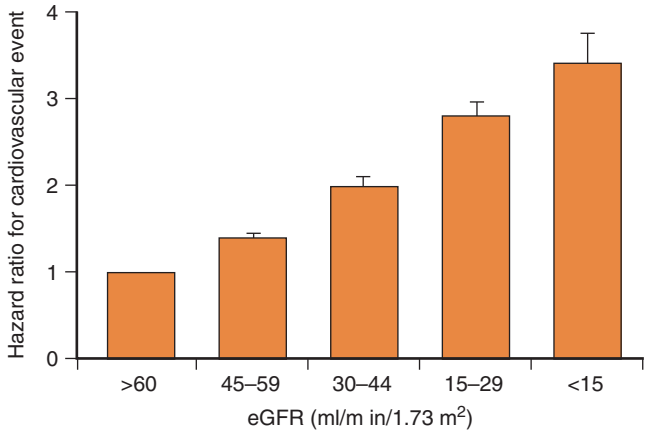


FIGURE 10-3 Hazard ratios for cardiovascular events according to the baseline eGFR, adjusted for baseline age, sex, income, education, coronary disease, chronic heart failure, stroke or transient ischemic attack, peripheral artery disease, diabetes, hypertension, dyslipidemia, cancer, hypoalbuminemia, dementia, liver disease, proteinuria, prior hospitalizations, and subsequent dialysis requirement. (Plotted using data in A.S. Go, G.M. Chertow, D. Fan, et al., Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, N. Engl. J. Med. 351 [13] [2004] 1296-1305.)

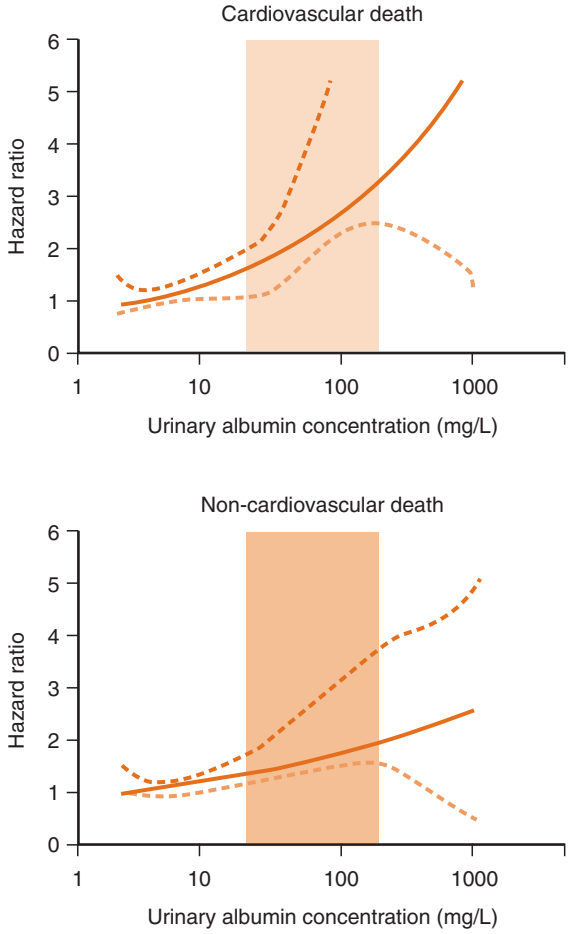


FIGURE 10-4 Microalbuminuria. Adjusted effect of urinary albumin concentration (UAC) on the hazard of cardiovascular and non-cardiovascular death. *Shaded areas* represent the upper and lower limit of current definition of microalbuminuria (20 to 200 mg/L). (Adapted from H.L. Hillege, V. Fidler, G.F. Diercks, et al., Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population, Circulation 106 [14] [2002] 1777-1782.)

Stage 1 to 2 Chronic Kidney Disease

Even in the absence of reduced eGFR, proteinuria, manifest as either micro- or macroalbuminuria, is associated with a higher prevalence of surrogates of CVD, including LVH in patients with hypertension,[24] arterial intima media thickening in patients with diabetes,[25] and brain white matter hyperintensity volume in the elderly.[26] Proteinuria, detected by a urine dipstick examination, was an independent risk factor for CVD outcomes in the Framingham cohort;[27,28] other studies have confirmed this finding in diabetic and hypertensive patients.[29,30] Lower levels of proteinuria have also been implicated as a risk marker for subsequent cardiovascular events. Microalbuminuria, defined by a urine albumin-to-creatinine ratio (ACR) of 30 to 300 mg/g, often marks early kidney damage due to diabetes, hypertension, or other conditions.[31] Secondary evaluation of the HOPE trial, evaluations of population-based cohorts in Norway and the Netherlands, and posthoc analysis of the LIFE study expanded on prior evaluations of proteinuria to show that microalbuminuria, even in very low quantities that are categorized as being in the normal range, are independently associated with CVD outcomes (Figure 10-4).[32–36]

RISK FACTORS

Cardiovascular disease risk factors are defined as characteristics, both modifiable and nonmodifiable, that increase the risk of developing CVD. Traditional CVD risk factors were identified in the Framingham Heart Study as conferring increased risk of CVD in the general population; these were later incorporated into prediction equations to aid physicians in identifying individuals at higher risk. Traditional risk factors include older age, male sex, hypertension, diabetes, smoking, and family history of coronary disease (Table 10-1).[37] Traditional cardiovascular disease risk factors are very common in

TABLE 10-1 Traditional and Nontraditional Cardiovascular Risk Factors

TRADITIONAL RISK FACTORS	NONTRADITIONAL FACTORS
Older Age	Albuminuria
Male sex	Lipoprotein (a) and apo (a) isoforms
Hypertension	Lipoprotein remnants
Higher LDL cholesterol	Anemia
Lower HDL cholesterol	Abnormal mineral metabolism
Diabetes	Volume overload
Smoking	Electrolyte imbalances
Physical inactivity	Oxidative Stress/Inflammation
Menopause	Malnutrition
Family history of cardiovascular disease	Thrombogenic factors
Left ventricular hypertrophy	Sleep disturbances
	Sympathetic tone
	Altered nitric oxide/endothelin balance

Reproduced and modified with permission from Sarnak MJ, Levey AS: Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 2000; 35(4 Suppl 1):S117-S131.

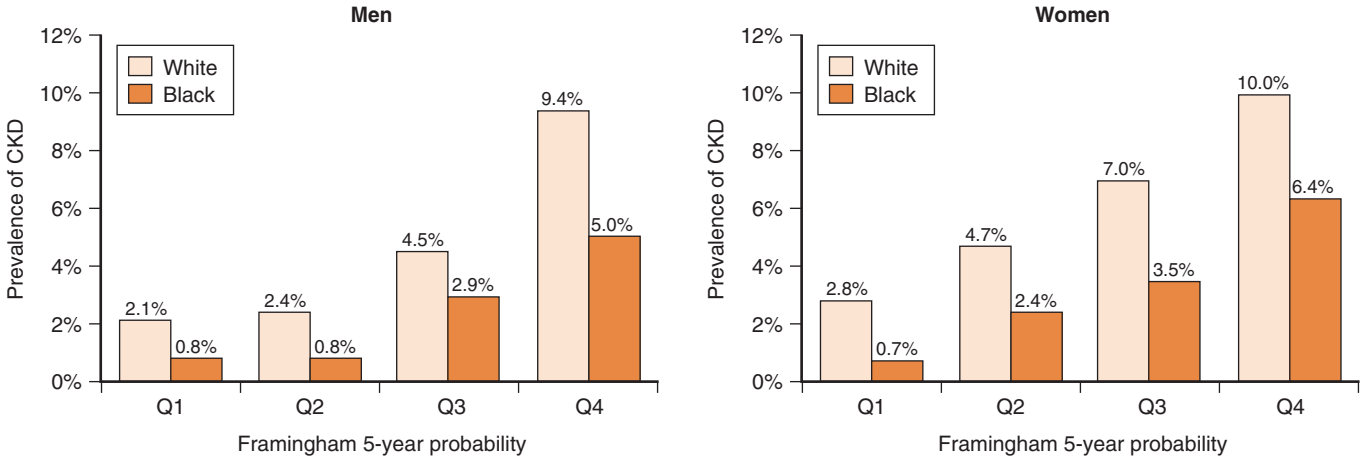


FIGURE 10-5 The prevalence of chronic kidney disease (CKD) based on the quartile of the Framingham risk score for developing coronary heart disease within 5 years, stratified by race in men and women. The *P* value for trend within each sex-specific race group is <0.001. (Adapted from D.E. Weiner, H. Tighiouart, J.L. Griffith, et al., Kidney disease, Framingham risk scores, and cardiac and mortality outcomes, Am. J. Med. 120 [6] [2007] 552 e1-e8.)

individuals with CKD, as suggested by higher coronary risk scores using the Framingham prediction equations in individuals with reduced kidney function (GFR <60 ml/min/1.73 m^2) (Figure 10-5).[38] Nontraditional risk factors include items that were not described in the original Framingham studies; nontraditional risk factors are those risk factors that both increase in prevalence as kidney function declines and have been hypothesized to be CVD risk factors in this population. Nontraditional risk factors may be particular to individuals with kidney disease (such as anemia and abnormalities in mineral metabolism) but also may include factors recognized as important in the general population (such as inflammation and oxidative stress).[39] Of note, the Framingham equations have poor discrimination and calibration in individuals with stage 3 to 4 CKD, perhaps reflecting either greater severity of traditional CVD risk factors or the role of nontraditional risk factors.[40]

MECHANISMS OF CARDIOVASCULAR DISEASE RISK IN CHRONIC KIDNEY DISEASE

There are several reasons why reduced GFR may be an independent risk state for CVD outcomes. These include, but are not limited to, residual confounding from traditional risk factors and insufficient adjustment for nontraditional risk factors. Additionally, reduced kidney function may be a marker of the severity of either diagnosed or undiagnosed vascular disease. Finally, patients with CKD may not receive sufficient therapy for their disease, including medications such as aspirin, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and diagnostic and therapeutic procedures.[41]

Similarly, there are several reasons why microalbuminuria may be an independent risk factor for CVD outcomes. Microalbuminuria may represent kidney disease itself, with an associated risk of subsequent CKD progression and development of macroalbuminuria. Microalbuminuria may also represent the kidney manifestation of systemic endothelial disease burden, or it may be associated with systemic inflammatory markers and abnormalities in the coagulation and fibrinolytic systems.[42]

Most CVD risk factors lead to atherosclerosis, arteriosclerosis, cardiomyopathy, or any combination of these three conditions (Table 10-2). Atherosclerosis, defined as an occlusive disease of the vasculature, and arteriosclerosis, defined as nonocclusive remodeling of the vasculature, may manifest as ischemic heart disease (IHD) and heart failure. Some risk factors, including dyslipidemia, primarily predispose to development and progression of atherosclerosis, whereas others, including volume overload and elevated calcium-phosphorus product, may predispose the patient to arteriosclerosis. Still other risk factors, including anemia and the presence of arteriovenous fistulae, may predispose the patient to cardiac remodeling and LVH. Essential to the understanding of CVD in CKD is an understanding of the interplay of these various risk factors. A simplified schematic of this interrelationship directed toward individuals with CKD not requiring kidney replacement therapy is displayed in Figure 10-6.

TRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Hypertension and Blood Pressure

Hypertension is both a cause and a result of kidney disease. About 70% to 80% of patients with stages 1 to 4 CKD have hypertension, and the prevalence of hypertension increases as GFR declines, such that over 80% to 90% of patients starting dialysis are hypertensive (Figure 10-7).[43–45]

Dialysis

There is a U-shaped relationship between blood pressure and CVD outcomes in the dialysis population, with increased CVD events and mortality at both markedly elevated postdialysis systolic blood pressures (>180 mmHg) and lower blood pressures (<110 mmHg) but no apparent increased risk at systolic blood pressure levels that would be consistent with severe hypertension in the general population (Figure 10-8).[46–48] However, higher blood pressures do not appear entirely benign in dialysis patients either;

TABLE 10-2 Spectrum of CVD in CKD: Differences from the General Population

TYPES OF CVD	PATHOLOGY	SURROGATES	CLINICAL PRESENTATIONS OF CVD
Arterial Vascular Disease	Atherosclerosis	Inducible ischemia, carotid IMT, EBCT (may be less useful than in the GP for atherosclerosis because of medial rather than intimal calcification), ischemia by ECG	IHD (myocardial infarction, angina, sudden cardiac death), cerebrovascular disease, PVD, HF
	Arteriosclerosis: Dilated and noncompliant large vessels	Aortic pulse wave velocity, calcification of the aorta, LVH (indirectly), increased pulse pressure	IHD, HF
Cardiomyopathy	Concentric LVH and LV dilatation with proportional hypertrophy	LVH, systolic dysfunction, and diastolic dysfunction by echocardiogram. LVH by ECG	HF, hypotension, IHD

(Reproduced with permission from M.J. Sarnak, A.S. Levey, A.C. Schoolwerth, et al., Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention, Circulation 108 [17] [2003] 2154-2169.)

CAD, coronary disease; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *EBCT,* electron beam computerized tomography; *ECG,* electrocardiogram; *GP,* general population; *HF,* heart failure; *IHD,* ischemic heart disease; *IMT,* intimamedia thickness; *LVH,* left ventricular hypertrophy; *LVMI,* left ventricular mass index; *PVD,* peripheral vascular disease.

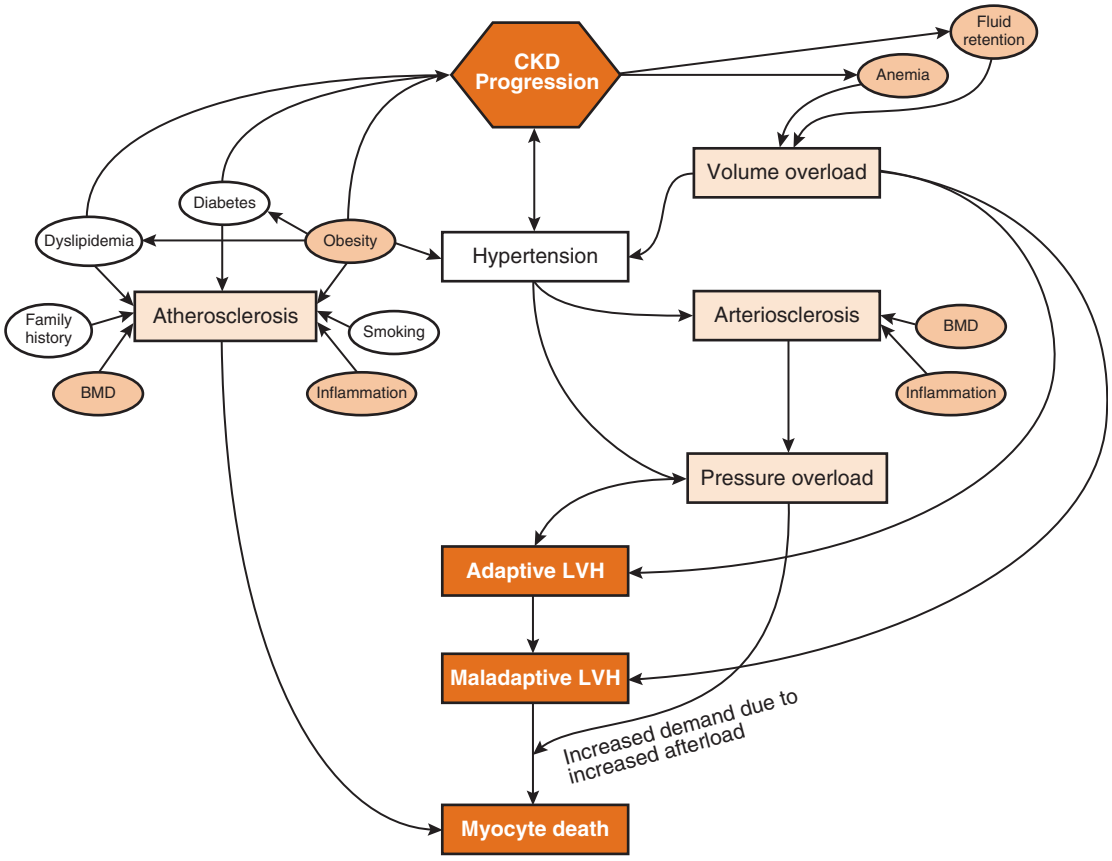


FIGURE 10-6 Concept diagram presenting a simplified overview of the relationship among chronic kidney disease, kidney disease risk factors, cardiovascular disease risk factors, and subsequent heart disease. Not all associations presented in this paradigm have been proven causal and, for simplicity, not all potential relationships are included. Selected traditional risk factors are presented in *white* and nontraditional risk factors are *shaded*. Outcomes, which themselves may be risk factors, are in *black*. Hypertension assumes a central role in this paradigm. *BMD,* bone and mineral disorder of CKD.

hypertension is an independent risk factor for IHD, LVH, heart failure,[49] and cerebral hemorrhage.[50] Unfortunately, in the absence of clinical trials delineating blood pressure targets in this population, there is no evidence supporting any blood pressure target or even the best means to achieve a specific blood pressure target, although ultrafiltration to dry weight is generally considered the initial treatment of hypertension.

There are two potential reasons why low blood pressure may be associated with adverse outcomes in dialysis patients: First, hypotension may be a reflection of the severity of other comorbid conditions including heart failure, cardiomyopathy and generalized malnutrition. Second, low blood pressure may predispose dialysis patients to intradialytic hypotension, which may lead to ischemic events.

Intradialytic hypotension is a relatively common occurrence during hemodialysis and may also be an independent marker for CVD outcomes, perhaps representing either the inability of the heart or blood vessels to appropriately compensate for reduced blood volume, or alternatively heart failure itself in the absence of overt volume overload.[51] Hypotension, particularly in the presence of reduced preload from ultrafiltration, may also represent the inability of a noncompliant left ventricle to compensate for decreased left ventricular filling pressures.

Stages 3 to 4 Chronic Kidney Disease

Blood pressure in stages 3 to 4 CKD has been investigated in more detail than in dialysis patients, although the focus of most studies has been on retarding progression of kidney disease rather than reducing CVD outcomes. Hypertension is highly prevalent in patients with CKD. In a Canadian evaluation of patients with creatinine clearance below 75 ml/min/1.73 m^2, 80% had hypertension (defined as blood pressure greater than 140/90 mmHg or use of antihypertensive medications),[52] whereas the prevalence of hypertension was 70% in the NHANES III population with CKD.[53] Hypertension was more commonly seen with CKD due to glomerular disease than tubulointerstitial disease.[54]

Elevated systolic blood pressure is an independent risk factor for CVD outcomes in both diabetic[55,56] and nondiabetic patients. A secondary analysis of the MDRD Study, which included a predominantly nondiabetic population, showed a 35% increased risk of hospitalization for CVD for each 10 mmHg increase in systolic blood pressure, and this increased risk remained significant even after adjusting for other traditional risk factors.[57] However, some of the added CVD risk may be driven by an increased rate of kidney disease progression associated with worse blood pressure control; for example, randomization to a lower blood pressure target in the MDRD study reduced the composite outcome of all-cause mortality and kidney failure 7 years after completion of the randomized intervention;[58] this was driven by fewer episodes of kidney failure.

Therapies for hypertension in CKD preferentially include ACE inhibitors and angiotensin receptor blockers (ARBs), often in conjunction with a diuretic. Several studies have shown a reduction in progression of CKD using ACE inhibitors and ARBs, particularly in patients with proteinuria.[35,59–64] Notably, in a subgroup analysis of patients with CKD in the HOPE study, ACE inhibitors were beneficial for reducing CVD events in patients with either preexisting vascular disease or diabetes combined with an additional cardiovascular risk factor.[21] Similarly, in a trial using losartan in individuals with diabetic nephropathy, losartan therapy was associated with a lower incidence of heart failure hospitalization,[65] whereas secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) showed that achievement of systolic blood pressure approaching a target of 120 mmHg was associated with a reduction in risk of most cardiovascular events, although achievement of even lower blood pressures was associated with increased risk.[66] These and similar findings resulted in a clinical practice recommendation by the Kidney Disease Outcomes Quality Initiative (K/DOQI) to target a blood pressure of less than 130/80 mmHg for CVD risk reduction in individuals with CKD and to use

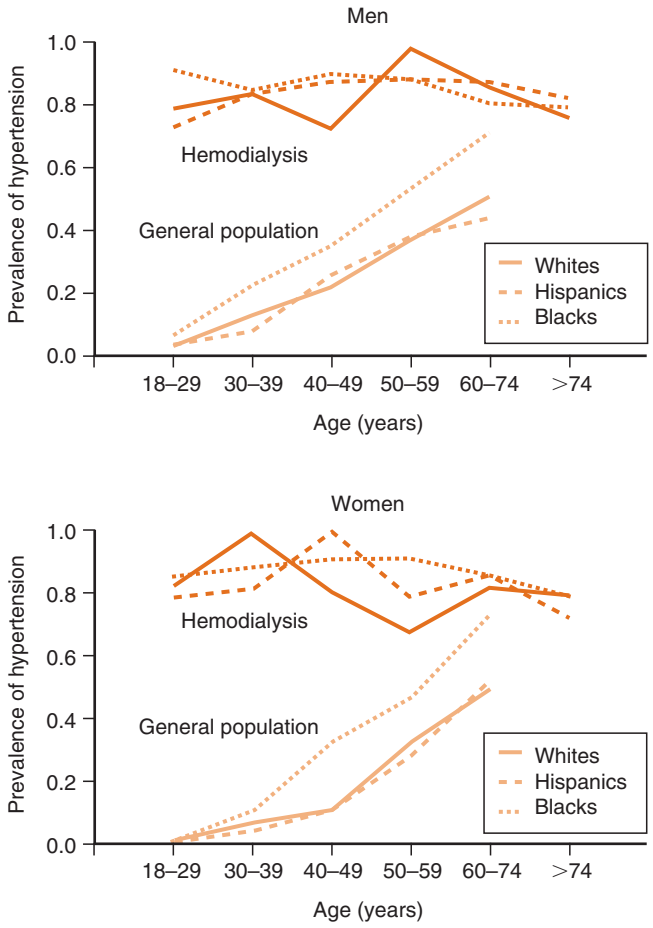


FIGURE 10-7 The prevalence of hypertension in chronic dialysis patients as compared to the general population. (Adapted from R. Agarwal, A.R. Nissenson, D. Batlle, et al., Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States, Am. J. Med. 115 [4] [2003] 291-297.)

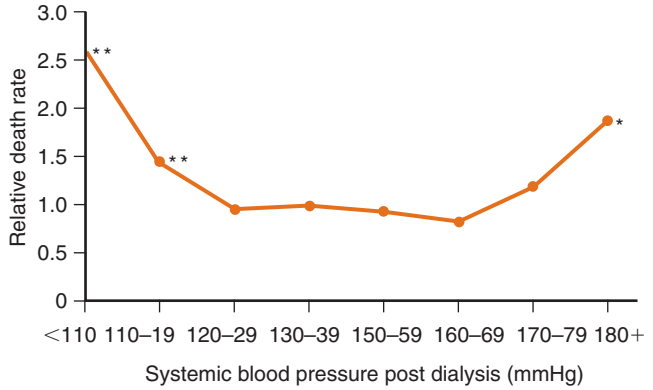


FIGURE 10-8 Systolic blood pressure postdialysis (SBP; time-varying) and CVD mortality in hemodialysis patients 1992 to 1996. The "U" curve relationship between SBP post dialysis and mortality is: SBP <110 mmHg, RR = 2.62; SBP 110 to 119 mmHg, RR = 1.48; SBP ≥ 180 mm Hg, RR = 1.96. P <0.01 for SBP <110 mmHg and p <0.05 for SBP between 110 and 119 and > 180 mmHg versus the reference group. (Adapted from P.G. Zager, J. Nikolic, R.H. Brown, et al., "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc, Kidney Int. 54 [2] [1998] 561-569.)

ACE inhibitors or ARBs as preferred agents in those with either diabetes mellitus or with a urine protein to creatinine ratio above 200 mg/g in a spot urine specimen.[67]

Dyslipidemia

Dyslipidemia is common in all stages of CKD, although the nature of dyslipidemia can be highly variable. As CKD progresses and kidney failure develops, levels of low-density lipoprotein (LDL) cholesterol that previously were high often normalize, perhaps reflecting worse nutritional status.[68]

Dialysis

In hemodialysis patients, high-density lipoprotein (HDL) cholesterol is typically low, whereas triglycerides are highly variable. Other abnormalities include increased levels of lipoprotein (a); a higher proportion of atherogenic, oxidized LDL cholesterol; and abnormal concentrations of apolipoproteins that comprise the major lipoproteins (Table 10-3). In peritoneal dialysis patients, the prevalence of hyperlipidemia, defined by elevated LDL cholesterol or triglyceride levels, is approximately 70%. Peritoneal dialysis patients have a somewhat more atherogenic lipid panel than their hemodialysis counterparts, with increased LDL-C, apolipoprotein B, oxidized LDL cholesterol, triglycerides, and lipoprotein (a) and decreased HDL cholesterol. Thus despite total cholesterol levels that may appear relatively normal in many patients (see Table 10-3), significant dyslipidemia is highly prevalent in the dialysis population.

Observational studies of dialysis patients have noted "reverse epidemiology" between cholesterol levels and risk of death, such that lower cholesterol levels are associated with a higher death rate.[69,70] For example, in an analysis of data from more than 12,000 hemodialysis patients predating widespread use of lipid lowering medications, individuals with low total cholesterol levels (<100 mg/dl) had a more than fourfold increase in risk of death compared to patients whose cholesterol levels were between 200 and 250 mg/dl.[71] Low cholesterol in these studies may be a surrogate for malnutrition and inflammation, suggesting that higher cholesterol levels may actually be associated with increased cardiovascular risk in dialysis patients with preserved nutritional status (e.g., serum albumin) and low levels of inflammatory markers (e.g., C-reactive protein).[70,72]

Results of the two major randomized controlled trials evaluating statins for the treatment of dyslipidemia in dialysis patients are discouraging. Both the German Diabetes and Dialysis Study (4D), which tested atorvastatin versus placebo in 1255 hemodialysis patients with diabetes, and AURORA, which tested rosuvastatin versus placebo in nearly 3000 hemodialysis patients, including both those with and without diabetes, failed to show a benefit with the lipid-lowering intervention despite successful lowering of LDL cholesterol.[73,74] Notably, neither study adequately evaluated younger dialysis patients who were likely to receive a transplant.

Stages 3 to 4 Chronic Kidney Disease

Earlier stages of CKD are often associated with diabetes, hypertension, cardiovascular disease and obesity—conditions that are frequently accompanied by dyslipidemia, in particular elevated LDL cholesterol and low HDL cholesterol. Additionally, the presence of nephrotic-range proteinuria can also exacerbate dyslipidemia.

For secondary prevention, data on treatment of dyslipidemia in individuals with stages 3 to 4 CKD are largely derived from posthoc analyses of clinical trials in the general population and generally show similar benefits to those seen in the general population.[75–77] A recent metaanalysis reviewing data through July 2006 demonstrated that: 1) statins significantly reduce lipid concentrations in patients with chronic kidney disease, irrespective of stage of disease; and 2) there is no definite benefit with statin therapy for reducing all-cause mortality, although cardiovascular endpoints occur less frequently in nondialysis patients with CKD.[78]

For primary prevention, this metaanalysis concluded that there were insufficient data in patients with later stages of CKD.[78] Since this metaanalysis, newer data emerged from a recent posthoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS), which evaluated the effect of atorvastatin on primary cardiovascular prevention in individuals with type 2 diabetes and eGFR below 60 ml/min/1.73 m^2 (stage 3 to 4 CKD). This analysis revealed a statistically significant 42% reduction in major cardiovascular events associated with use of atorvastatin; however, there was no significant impact of atorvastatin on all-cause mortality.[79]

TABLE 10-3 Lipid Abnormalities by Target Population (Approximate Percentage)

	TOTAL CHOLESTEROL > 240 mg/dl	LDL CHOLESTEROL > 130 mg/dl	HDL CHOLESTEROL < 35 mg/dl	TRIGLYCERIDES > 200 mg/dl
General Population*	20	40	15	15
CKD Stages 1 to 4†				
With Nephrotic Syndrome‡	90	85	50	60
Without Nephrotic Syndrome‡	30	10	35	40
CKD Stage 5†				
Hemodialysis	20	30	50	45
Peritoneal Dialysis	25	45	20	50

B.L. Kasiske, Hyperlipidemia in patients with chronic renal disease, Am. J. Kidney Dis. 32 (5 Suppl. 3) (1998) S142-S156.
*Data from National Health and Nutrition Examination Survey (NHANES) III and the Framingham Offspring Study.[245,246]
†Data extracted from multiple observational studies.[244]
‡Nephrotic proteinuria was defined as > 3 g of total protein excretion in 24 hours.

TABLE 10-4 Treatment Recommendations for Dyslipidemia in CKD Patients*

DYSLIPIDEMIA	TREATMENT GOAL	INITIAL REGIMEN	INCREASED REGIMEN	ALTERNATIVE REGIMEN
TG $\geq$ 500 mg/dl†	TG < 500 mg/dl	TLC	TLC + Fibrate or Niacin	Fibrate or Niacin
LDL 100–129 mg/dl	LDL < 100 mg/dl	TLC	TLC + low dose statin	Bile acid sequestrant or Niacin
LDL $\geq$ 130 mg/dl	LDL < 100 mg/dl	TLC + low dose statin	TLC + max. dose statin	Bile acid sequestrant or Niacin
TG $\geq$ 200 mg/dl and non-HDL $\geq$ 130 mg/dl	Non-HDL < 130 mg/dl	TLC + low dose statin	TLC + max. dose statin	Fibrate or Niacin

Adapted with permission from C. Zoccali, F.A. Benedetto, F. Mallamaci, et al., Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis, J. Am. Soc. Nephrol. 12 (12) (2001) 2768-2774.
HDL, high-density lipoprotein cholesterol; *LDL,* low-density lipoprotein cholesterol; *TG,* triglycerides; *TLC,* therapeutic lifestyle changes.
*This guideline precedes publication of 4D and AURORA in dialysis patients; based on those studies, there are no clinical trial data to support statin use in most hemodialysis patients.
†Combined therapy with a statin and a fibrate is contraindicated in late stage CKD due to an increased risk of rhabdomyolysis.

Data on primary prevention in earlier stages could be expected to mirror that in the general population; however, the PREVEND study failed to demonstrate a reduction of CVD events with pravastatin versus placebo in individuals with predominantly stage 1 and stage 2 CKD (microalbuminuria). Admittedly only 864 individuals were included in the study, which, along with the 2 × 2 factorial design, does raise the possibility of insufficient power.[80]

Current Recommendations

In 2003, the National Kidney Foundation (NKF) published K/DOQI guidelines for the treatment of dyslipidemia in CKD. These reflect a paucity of trial data and primarily were based on expert opinion. Summarized in Table 10-4, these guidelines suggested that all patients with CKD, even in the absence of known CVD, be considered at high risk for CVD outcomes and recommended treatment of lipid levels similar to that recommended for the general population (namely LDL-C < 100 mg/dl and non-HDL-C < 130 mg/dl).[81] Taken in sum with more recent studies, we would suggest that the K/DOQI guideline is potentially valid for individuals with stage 3 CKD, but does not apply to hemodialysis patients, particularly those with expected remaining lifespan of less than 5 years. Evidence is altogether lacking for individuals receiving peritoneal dialysis. The ongoing Study of Heart and Renal Protection (SHARP), a randomized trial comparing combined therapy to simvastatin and ezetimibe to placebo in approximately 6000 stage 3 and 4 CKD patients and another 3000 dialysis patients, will hopefully offer guidance for treating dyslipidemia in individuals with late stage CKD.[82]

Diabetes Mellitus

Diabetes is the leading cause of kidney failure in the United States. The annual incidence of ESRD in the United States due to diabetes now sits at 159 per million—for context this is similar to the rate of HIV infection (185 per million) and exceeds the incidence rates of both pancreatic and ovarian cancers in the United States.[83,84] Based on medical evidence forms, 52.6% of incident ESRD patients in the United States have diabetes, and it is the primary cause of ESRD in 43.6% of patients.[1] Diabetes in CKD is extensively discussed in Chapter 11 and will only be briefly reviewed here.

In dialysis patients, the presence of diabetes is an independent risk factor for ischemic heart disease, heart failure, and all-cause mortality.[85,86] Dialysis patients with diabetes also have worse long-term outcomes following coronary interventions than do nondiabetic patients with CKD.[87,88] Notably, the net benefit of rigid diabetes control is uncertain in the dialysis population because microvascular and macrovascular complications already exist and because of a potentially increased risk of hypoglycemia; however, hyperglycemia may still worsen retinopathy, hasten the loss of residual kidney function, cause or worsen peripheral neuropathy, and increase the risk of infection. Two large, observational studies have examined the association between glycosylated hemoglobin level and outcomes in hemodialysis patients. In an analysis of Fresenius data, there was no relationship between glycosylated hemoglobin level and mortality at 1 year;[89] similarly, in an analysis of DaVita data, there was no significant increased risk of mortality until glycosylated hemoglobin levels rose above 8%, at which time increased mortality risk was only appreciated after extensive multivariable adjustment for case-mix, nutritional, and inflammatory factors.[90] Notably, this result was driven by cardiovascular mortality and was only seen in individuals with hemoglobin levels stable and 11 g/dl or more; the authors theorized that this relationship was not seen at lower hemoglobin levels due to the effect of atypical red blood cell production and turnover on glycosylated hemoglobin values in hemodialysis patients with variable hemoglobin levels. Reflecting the notable lack of studies in the dialysis population of the relationship between glycemic control and CVD outcomes, currently there is no evidence-based recommendation from K/DOQI or KDIGO regarding diabetes management in dialysis patients.[91]

For individuals with earlier stages of CKD, diabetes mellitus is one of the leading causes of kidney disease, with microalbuminuria the first clinical manifestation of diabetic nephropathy. In the general population, diabetes is a powerful risk factor for cardiovascular outcomes.[92] The same holds true for patients with CKD, where the presence of diabetes is a leading risk factor for cardiovascular events and all-cause mortality.[13,40] Diagnosis and management of diabetes in individuals with earlier stage CKD, including review of the recent K/DOQI guideline, are extensively discussed in Chapter 11.

Left Ventricular Hypertrophy

LVH is highly prevalent in both stages 3 and 4 CKD and dialysis patients and represents a physiological adaptation to a long-term increase in myocardial work requirements.

LVH can be considered both a traditional risk factor, reflecting its inclusion in the original Framingham prediction instrument, and a cardiovascular outcome.

Epidemiology

LVH is very common in CKD patients, with prevalence rates of approximately 30% in stage 3 CKD, 45% in stage 4 CKD, and as high as 70% in incident dialysis patients;[5] this likely reflects the confluence of risk factors predisposing to pressure and volume overload. Among prevalent dialysis patients, LVH is present in 50% to 75% of patients when assessed by echocardiography.[93,94] LVH is even seen in the majority of children requiring hemodialysis, where typically there is an absence of ischemic heart disease.[95] As in the general population, LVH is an independent risk factor for adverse CVD outcomes in dialysis patients;[96,97] this holds true for both concentric LVH and dilated cardiomyopathy.[98]

Pathogenesis

LVH may result from either pressure or volume overload, and it reflects an appropriate adaptation by the heart to these forces (Table 10-5, see Figure 10-6). Increasing cardiac workload may be a tenet of CKD, reflecting increased volume retention and blood pressure accompanying deteriorating kidney function. As workload rises over time, increased oxygen demands by the hypertrophied left ventricle may ultimately exceed its perfusion, resulting in ischemia and eventual myocyte death. In later-stage CKD and dialysis patients, this inability to increase cardiac perfusion is a reflection not only of the LVH but also the high prevalence of both atherosclerosis and arteriosclerosis limiting the ability of the vasculature to upregulate supply to compensate for increased demand. The endstage of this process is cardiomyopathy.

Pressure overload results from increased cardiac afterload, often due to hypertension, aortic stenosis, and reduced arterial compliance from arteriosclerosis.[99,100] Some evidence also suggests that increased vascular calcification in dialysis patients may also contribute to this phenomenon.[100] Volume overload may be related to anemia, as the heart attempts to compensate for decreased peripheral oxygen delivery.[101,102] Other causes of volume overload include increased extracellular volume seen in CKD[103,104] and the presence of arteriovenous fistulae.[105]

Often LVH is initially concentric, representing a uniform increase in wall thickness secondary to pressure overload from hypertension or aortic stenosis. The concentric thickening of the wall of the left ventricle allows for generation of greater intraventricular pressure, effectively overcoming increased afterload. Volume overload may result in eccentric hypertrophy secondary to the addition of new sarcomeres in series. Eccentric hypertrophy is defined by an increased LV diameter with a proportional increase in LV wall thickness. The initial physiology often is consistent with diastolic dysfunction. As this process progresses, capillary density decreases and subendocardial perfusion is reduced. Myocardial fibrosis may ensue and, with sustained maladaptive forces, myocyte death occurs. In its extremes, the endpoint of this cycle can be dilated cardiomyopathy with eventual reduction in systolic function (see Figure 10-6).[98]

Diagnosis

Diagnosis of LVH is readily accomplished with echocardiography.[91] Cardiac function is best assessed in the euvolemic state, as significant volume depletion and overload both reduce left ventricular inotropy.[106] Accordingly, in dialysis patients, two-dimensional echocardiogram results may be most meaningful on the interdialytic day, whereas three-dimensional echocardiography may be useful to assess LV structure as it avoids the use of geometric assumptions of LV shape that are required to estimate LV mass and volume that are used for interpreting two-dimensional echocardiograms.[107] Magnetic resonance imaging may be more precise for assessing LV structure than echocardiography, but this technique is not yet widely available and the costs may be prohibitive.[108,109] Although screening echocardiography is currently recommended for incident dialysis patients, there is no evidence to date that this results in improvement in clinical outcomes.[91]

Therapy

Given the complexity of its development, LVH presents a challenging target for therapy. Potentially modifiable risk factors for LVH (and subsequent heart failure) include anemia, hypertension, extracellular volume overload, abnormal mineral metabolism, and arteriovenous fistulae.[110] It is notable that in CKD patients there is a paucity of trial data showing a mortality benefit associated with treating many of these LVH risk factors.

Data from several small observational studies and nonrandomized trials have suggested that regression of LVH can be induced by modification of risk factors including anemia and systolic blood pressure and strict management of volume using treatment modalities like daily dialysis.[104,111–114] However, multiple randomized trials, including studies in both dialysis patients and patients with stages 3 to 4 CKD, have not demonstrated regression of LVH or a decrease in LV mass with near-normalization of hemoglobin.[115–118]

Current treatment for LVH focuses on afterload reduction and volume management; accordingly ACE inhibitors or ARBs, often in conjunction with diuretics, are a mainstay of treatment.[119] Other therapy at this time is best directed at modifying the multiple risk factors for LVH to prevent its development, particularly in the predialysis CKD population.

TABLE 10-5 Causes, Risk Factors, and Manifestations of Left Ventricular Hypertrophy (LVH) in CKD

LVH RISK FACTOR	PHYSIOLOGY/ETIOLOGY	INDICATORS/DIAGNOSTIC TEST	CLINICAL SEQUELAE
Pressure overload	Reflects increased afterload due to hypertension, valvular disease (predominantly aortic valve), arteriosclerosis	Echocardiography Cardiac MRI Electrocardiography	Myocardial infarction Angina Sudden cardiac death Heart failure
Volume overload	Reflects volume retention due to progressive kidney disease +/− anemia		

MRI, magnetic resonance imaging.

Other Traditional Risk Factors

Other traditional risk factors include advanced age, male sex, and smoking. Of these, only smoking presents an opportunity for intervention.[120] Although there have been few studies examining specific effects of smoking in dialysis patients, a evaluation of U.S. Renal Data System (USRDS) data showed that smoking was a strong, independent risk factor for incident heart failure, incident peripheral vascular disease, and all-cause mortality. Importantly, dialysis patients who were former smokers were more similar to nonsmokers than current smokers in risk, demonstrating the potential benefit of smoking cessation efforts in dialysis patients.[121]

NONTRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Oxidant Stress and Inflammation

Oxidant stress has been proposed as a unifying concept linking both traditional and other nontraditional risk factors in CKD.[122] Oxidant stress may be defined as an imbalance between prooxidants and antioxidants (oxidant defenses) that leads to tissue damage.[123] Most oxidation occurs in the mitochondria, although phagocytes also induce production of reactive oxygen species (ROS) in a "respiratory burst" designed to defend the body against infection. ROS can oxidize lipids, proteins, carbohydrates, and nucleic acids, which can then be measured as markers of oxidant burden. This system is balanced by a series of antioxidant defenses, some of which work by enzymatically catalyzing reduction of oxidant species (e.g., superoxide dismutase, catalase), whereas others work nonenzymatically by scavenging for oxidants (e.g., glutathione, vitamin C).[124] There is also a complicated interplay between ROS and advanced glycation end-products (AGEs) in CKD,[125] such that ROS may be both a cause and consequence of AGE formation in individuals with diabetes and with CKD, and AGE accumulation may result in tissue damage and further oxidative and inflammatory stress.

Numerous factors in CKD patients increase oxidant stress, including inflammation, malnutrition (by reducing antioxidant defenses), uremic toxins, and potentially the dialysis procedure itself. Patients with CKD not only have higher levels of oxidant stress, they also have decreased defenses, particularly plasma protein-associated free thiols such as glutathione.[122] This "double-hit" makes CKD patients particularly vulnerable to sequelae of oxidant stress.

The lesions of atherosclerosis may represent a sequence of inflammatory processes affecting the vasculature, as elevated and modified LDL cholesterol, genetic factors, infectious microorganisms, free radicals caused by cigarette smoking, hypertension, diabetes mellitus, ischemic injury, and combinations of these all predispose the patient to progressive endothelial dysfunction.[126] These factors are all common in individuals with CKD. In the general population, inflammation is a reasonably well-established risk marker for CVD, with leukocytosis and c-reactive protein (CRP) both independently associated with adverse cardiovascular outcomes.[127] In dialysis patients, several studies have demonstrated a strong, independent association between inflammation and the risk of adverse CVD outcomes.[93,128–130] In stages 3 to 4 CKD, inflammatory markers, including CRP, elevated white blood cell count, and fibrinogen, are associated with adverse cardiovascular outcomes;[131,132] however, there is no significant difference in the magnitude of risk associated with inflammatory markers when comparing individuals with eGFR below and above 60 ml/min/1.73 m^2.[131]

At this time, specific strategies to treat oxidant stress and inflammation in CKD have not been adopted, although potential therapies may be forthcoming. For example, statins are associated with a greater beneficial effect on CVD events and mortality than would be expected by changes in the lipid profile alone in the general population;[133] However, although statins may decrease CRP levels in dialysis patients, there is no evidence of a survival benefit associated with their use.[73,74]

Numerous studies have investigated the use of antioxidants for cardiovascular protection in the general population, the most notable of which demonstrated no benefit of vitamin E supplementation.[134] However, in dialysis patients, a study of 200 patients with prevalent CVD demonstrated a benefit associated with daily use of 800 international units of vitamin E,[135] whereas a separate study showed a benefit with use of 600 mg of acetylcysteine twice daily.[136] Other investigations have used vitamin E-coated dialyzers and noted a decrease in oxidant stress.[137,138] Overall these studies remain preliminary and have not been consistently reproduced.

Nitric Oxide, Asymmetrical Dimethylarginine, and Endothelial Function

Adequate nitric oxide production is critical for local vascular regulation and endothelial function. In individuals with CKD, nitric oxide production is reduced, likely reflecting substrate (L-arginine) limitation and increased levels of circulating endogenous inhibitors of nitric oxide synthase (NOS), most notably asymmetrical dimethylarginine (ADMA). ADMA is a competitive inhibitor of NOS and is chiefly metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to citrulline and dimethylamine. In kidney disease, particularly in states of high oxidative stress, DDAH activity is reduced, resulting in higher plasma and tissue levels of ADMA.[139] Accordingly, the relationship among nitric oxide, endothelial function, and kidney disease may be another example of a vicious circle in this patient population, with chronic NOS inhibition causing systemic and glomerular hypertension, proteinuria, and glomerular and tubular injury, with these ultimately resulting in progressively worse kidney function that leads to further reductions in nitric oxide availability.[139] One cross-sectional study explored these relationships, demonstrating an independent association between higher ADMA levels and lower eGFR, between ADMA levels and reduced coronary flow reserve, and between lower eGFR and reduced coronary flow reserve, with the highest ADMA levels seen in individuals with both lower eGFR and reduced coronary flow reserve.[140] This observation requires further exploration in longitudinal analyses across a broader range of GFR levels.

Higher ADMA levels have been noted in individuals with earlier stages of CKD and continue to rise as the GFR declines. Higher ADMA levels are associated with more

rapid kidney function decline and all-cause mortality in people with kidney disease.[141,142] Furthermore, ADMA has been independently associated with increased cardiovascular risk in both the stage 3 to 4 CKD and dialysis populations. In a posthoc analysis of the MDRD Study, each 0.25 μmol/L increase in ADMA levels was associated with both a 31% higher prevalence of cardiovascular disease after adjusting for traditional and nontraditional risk factors and borderline statistically significant 9% and 19% increases in all-cause mortality and CVD mortality, respectively.[143] Similarly, in a cohort of 225 chronic hemodialysis patients, each 1 μmol/L was associated with a statistically significant 26% increase in all-cause mortality and a 17% increase in incident cardiovascular events.[144] This research has established important groundwork for potentially addressing one aspect of increased cardiovascular risk in CKD. However, there has been no pharmacological intervention to date that reliably reduces ADMA levels in individuals with CKD.[145–147] Accordingly, cardiovascular risk reduction targeting nitric oxide and ADMA remains an active area of research.

Homocysteine

Homocysteine, a metabolite of the essential amino acid methionine, has been implicated in observational studies in the general population as a risk factor for myocardial infarction and stroke.[148,149] Homocysteine levels increase as GFR declines,[150] and hyperhomocysteinemia is much more common in dialysis patients than in the general population. Further, as elevated levels of homocysteine can often be reduced using pharmacological doses of B vitamins, it is an attractive potential nontraditional risk factor. To date, there have been multiple large randomized trials of homocysteine-lowering therapies that enrolled patients at high risk of cardiovascular disease outcomes in the general population and late stage CKD and dialysis patients, which, despite successful lowering homocysteine levels, have failed to demonstrate a reduction in cardiovascular events.[151–156] Accordingly, there are no data to suggest a benefit to homocysteine-lowering with B vitamins.

Chronic Kidney Disease-Mineral Bone Disorder

Chronic kidney disease-mineral bone disorder (CKD-MBD) is an important nontraditional risk factor for cardiovascular disease in individuals with stages 3 to 5 CKD. The hypothesis that vascular calcification contributes to cardiovascular disease burden in CKD is supported by several studies in dialysis patients that show independent associations between coronary artery calcification with mortality[157] and between both peripheral artery intimal and medial calcification with mortality.[158]

Arterial calcification, and specifically medial calcification, is far more common in individuals with CKD than in the general population,[159,160] likely reflecting a complex interrelationship among hyperphosphatemia, secondary hyperparathyroidism, vitamin D deficiency, and other markers of mineral metabolism that, in conjunction, serve to overwhelm natural defenses against calcification (Table 10-6).[161] A model suggesting that vascular calcification occurs in patients with decreased plasma levels of inhibitory proteins, including fetuin-A, osteoprotegerin, and matrix Gla protein, has been extensively tested, but, to date, these proteins have not been consistent markers of calcification.[162] Additional proteins that may affect this interrelationship include fibroblast growth factor-23 (FGF-23), a phosphatonin that decreases renal phosphate reabsorption, and klotho, a protein facilitating the binding of FGF-23 to its receptor.[163]

As seen with the other nontraditional risk factors, there are extensive observational data implicating vascular calcification and effectors of vascular calcification in the pathogenesis of CVD in individuals with CKD. Providing a physiological basis for the hypotheses that abnormal calcium and phosphorus handling impacts vascular calcification, in vitro studies have linked increased vascular calcification to both hyperphosphatemia[164,165] and hyperparathyroidism,[166] and they have shown that less vascular calcification accompanies low to moderate doses of vitamin D receptor activators.[167]

Multiple longitudinal studies, including an evaluation of DOPPS data, have demonstrated increased cardiovascular

TABLE 10-6 Currently Hypothesized Mediators of Arterial Calcification in CKD

FACTOR	REGULATION	STATUS IN CKD	HYPOTHESIZED ROLE IN VASCULAR CALCIFICATION
		PRECIPITANTS	
Phosphorus	Dietary intake, phosphorus binders, vitamin D, FGF23/klotho, parathyroid hormone	↑↑↑	Passive precipitation of product with calcium, higher intracellular phosphate induces osteogenic behavior of VSMCs
Calcium	Parathyroid hormone, dietary intake, vitamin D	↔	Passive precipitation of product with phosphorus, higher intracellular calcium induces osteogenic behavior of VSMCs
		CALCIFICATION INHIBITORS	
Fetuin A	Negative acute phase reactant	Variable	Inhibits local precipitation of calcium and phosphorus
Osteoprotegerin	Modulates osteoclast activation by indirectly preventing RANKL binding	Likely ↑, (but relative deficiency)	Local inhibition of cartilage and vascular calcification
Matrix Gla protein	Activated by vitamin K-dependent γ-carboxylation, (warfarin reduces active MGP)	Likely ↑, (but relative deficiency)	Local inhibition of cartilage and vascular calcification

RANKL, receptor activator of NF-kB ligand; VSMC, vascular smooth muscle cell.

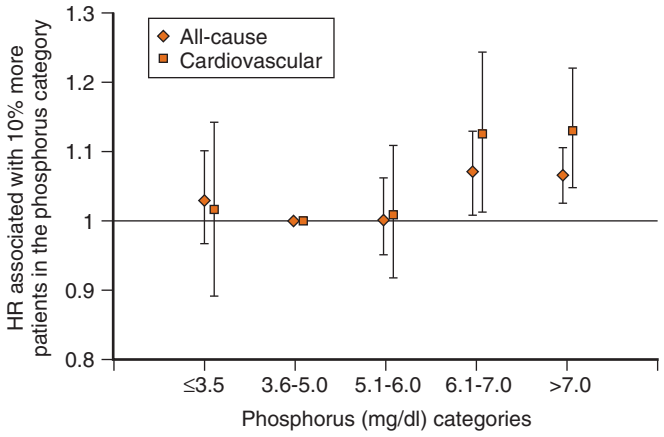


FIGURE 10-9 Individual patient all-cause and cardiovascular mortality risk associated with 10% more facility patients within each serum phosphorus category versus the reference category of 3.6 to 5.0 mg/dl in the DOPPS I, II and III cohorts. Hazard ratios (HRs) reflect models stratified by study phase and region and adjusted for facility clustering effect; baseline patient age, sex, race, body mass index, time with ESRD, comorbid conditions, hemoglobin level, albumin level, normalized protein catabolic rate, single-pool Kt/V, prior parathyroidectomy, and vitamin D prescription; percentage of patients at a facility with serum calcium levels of 8.5 or less, 8.6 to 10, and greater than 10 mg/dl; and percentage of patients at a facility with serum parathyroid hormone (PTH) levels of 100 or less, 101 to 300, 301 to 600, and greater than 600 pg/ml. (Adapted from F. Tentori, M.J. Blayney, J.M. Albert, et al., Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study [DOPPS], Am. J. Kidney Dis. 52 [3] [2008] 519-530.)

and all-cause mortality with higher serum phosphate levels, supporting this hypothesis (Figure 10-9), with the greatest mortality risks associated with serum calcium levels above 10 mg/dl, phosphorus levels greater than 7.0 mg/dl, and PTH levels greater than 600 pg/ml.[168] Similarly, other large dialysis cohorts have shown worse outcomes in the presence of lower vitamin D levels and benefit associated with vitamin D analogue use.[169,170] These data are reviewed in more detail in Chapter 9. However, the major shortcoming in all of these studies to date is an inability to determine causality.

Again, similar to that seen with the other nontraditional risk factors, there is a paucity of clinical trial data associating management of CKD-MBD with improved cardiovascular and mortality outcomes. Although observational studies suggest that vitamin D analogues, phosphorus binders versus placebo, and non-calcium–containing binders versus calcium-containing phosphorus binders all reduce vascular calcification in CKD stages 3 to 5,[170–173] trial data have not consistently supported a benefit for hard cardiovascular or mortality outcomes for any of these interventions; in particular, the interpretation of studies evaluating phosphate binder selection remains controversial.[157,174,175]

Other Nontraditional Risk Factors

Other nontraditional risk factors for CVD include anemia (Chapter 7), lipoprotein abnormalities, sympathetic tone, malnutrition, and sleep abnormalities.[176] Some of these issues are discussed at length elsewhere in this text, and anemia, in part, is referred to in the discussion of LVH above.

CARDIOVASCULAR DISEASE SYNDROMES

Ischemic Heart Disease

Epidemiology

As discussed earlier, IHD is common in patients with stages 3 to 4 CKD and in dialysis patients. In dialysis patients, an analysis of the USRDS Dialysis Morbidity and Mortality Study (DMMS) Wave 2 showed that the incidence of hospitalizations for acute coronary syndromes was 29 per 1,000 person years and the incidence of AMI was 19 per 1,000 person years.[177] Outcomes for dialysis patients with AMI are abysmal with 50% 1-year mortality and an 80% 3-year mortality,[177] whereas outcomes following coronary interventions are similarly bad, with 50% mortality at 2.5 years after coronary bypass surgery.[178] Outcomes among individuals with nondialysis late stage CKD are also poor, with adjusted 8-year survival rates of 45.9% with coronary bypass surgery, 32.7% with percutaneous coronary artery intervention, and 29.7% with no revascularization therapy among all patients with serum creatinine greater than 2.3 mg/dl who underwent coronary angiography between 1995 and 2001 in Alberta, Canada. These mortality rates were strikingly similar to those seen with dialysis patients in the same study and contrast with patients in the same study with serum creatinine levels below 2.3 mg/dl, where adjusted 8-year survival rates were 85.5%, 80.4%, and 72.3%, respectively.[179]

Pathophysiology and Manifestations: Atherosclerosis and Arteriosclerosis

Arterial disease in individuals with CKD can be broadly classified as relating to atherosclerosis, which is a focal process of plaque formation resulting in luminal narrowing, and arteriosclerosis, which is a diffuse process of arterial stiffening resulting in increased systolic blood pressure and pulse pressure and compensatory left ventricular hypertrophy in the setting of increased afterload (see Table 10-2). In most cases, it is the interplay between atherosclerosis and arteriosclerosis often accompanied by resultant LVH that yields clinically apparent ischemic cardiovascular disease.[180]

Atherosclerosis in CKD, particularly in individuals with advanced CKD, has been dubbed "accelerated" in efforts to explain the high prevalence. Atherosclerosis in CKD may be a manifestation of increasingly severe risk factors that are prevalent as kidney disease progresses, including a highly atherogenic lipid profile.[181] Importantly, IHD may be present without significant atherosclerosis. In one study, up to 50% of nondiabetic dialysis patients with symptoms of myocardial ischemia did not have significant large caliber coronary artery disease.[182] The authors of this study hypothesized that the patients may have ischemia secondary to the combined effects of volume overload and LVH causing increased myocardial oxygen demand, and small and larger vessel arterial disease, decreased capillary density, and potentially anemia all causing decreased oxygen supply.

Arteriosclerosis or arterial stiffness is a state of reduced arterial compliance characterized by diffuse dilatation and hypertrophy of large arteries with loss of arterial elasticity; this commonly occurs in aging but is far more profound in

CKD and is potentially related to the high prevalence of hypertension and disorders of mineral metabolism that promote arterial calcification.[159] Arteriosclerosis likely has its onset in the early stages of CKD[58] and is often present at the time of dialysis initiation.[183]

Manifestations of arteriosclerosis in CKD patients include LVH and changes in the blood pressure profile. Specifically, with loss of arterial elasticity, increased systolic blood pressure with or without a decrease in diastolic blood pressure is common. This results in an increased pulse pressure, which is an independent risk factor for mortality in dialysis patients.[184,185] Other tests that may be more sensitive for identifying the arteriosclerotic phenotype include measures of aortic pulse wave velocity and augmentation index;[186] abnormal aortic pulse wave velocity and augmentation index are both associated with increased mortality in dialysis patients.[187] Accordingly, the role of CKD and, in particular, the dialysis milieu in promoting arteriosclerosis were nicely demonstrated in a report of 14 children receiving hemodialysis who had markedly increased aortic pulse wave velocity and augmentation index compared to controls.[160]

An additional factor that may be important is the concept of capillary density and cardiomyocyte dropout. In animal models of CKD, a reduction in the number of cardiomyocytes and hypertrophy of the remaining myocytes has been appreciated with lower eGFR,[188] whereas, in a small autopsy study, myocardial capillary density was significantly lower in patients with kidney failure receiving dialysis than in patients with essential hypertension and normotensive controls.[189] Taken in sum with recognition of atherosclerotic and arteriosclerotic disease in individuals with kidney disease, it is likely that cardiac ischemia in many patients with CKD represents a multifactorial process with synergistic interaction among disease phenotypes.

Diagnosis

Although IHD is extremely common in CKD, routine screening is not currently recommended in the absence of clinical manifestations of CVD. Available diagnostic tools are similar to those used in the general population and include resting echocardiography for evaluation of cardiac structure and function, exercise and pharmacological stress testing for detection of perfusion defects, laboratory tests for assessment of both acute ischemia and chronic cardiac risk, and cardiac catheterization for anatomical description and possible repair of coronary anatomy. There is no single test for identifying IHD in patients with CKD, and each test currently in use has disadvantages specific to CKD that may affect sensitivity and specificity. The best initial option to identify cardiac ischemia is likely a functional assessment of perfusion that includes cardiac imaging (given the high prevalence of baseline ECG abnormalities in CKD patients); readily available options include exercise or pharmacological nuclear stress tests and exercise or pharmacological stress echocardiography. As a single test, stress echocardiography, either exercise or pharmacological if exercise is not feasible, may be particularly useful as echocardiography also provides information on valvular and other structural disease.[190] Although individuals with CKD represent a higher risk population for complications of angiography, including bleeding and restenosis with or without stenting, there is no absolute contraindication to cardiac catheterization in CKD.[191] Although preservation of existing kidney function is an important consideration in all stages of kidney disease, including for those receiving dialysis, many individuals with stage 3 and stage 4 CKD can avoid significant contrast nephropathy, with careful management and conservative use of iodinated contrast.[191]

Several other noninvasive imaging tests may identify coronary disease or increased risk of coronary disease. These include increased intima-media thickness of the carotid wall that is detectable by ultrasound and that may correlate with disease in other arterial beds.[192,193] Additionally, electron beam computerized tomography (EBCT) has also emerged as a sensitive method to detect vascular calcification that correlates with atherosclerosis and predicts development of coronary artery disease in the general population.[194] However, EBCT may not be an ideal method to detect atherosclerosis in CKD because it is unable to distinguish between intimal calcifications of atherosclerosis and medial calcification that is common in CKD.[195]

Laboratory evaluation of coronary syndromes in CKD patients also is challenging, as many of the markers used in the general population, including cardiac troponin I and T, N-Terminal pro-B-type natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), creatine kinase (CK) and the MB subfraction of creatine kinase (CK-MB), and myoglobin all may be chronically elevated. For example, 20% of asymptomatic hemodialysis patients have cardiac troponin T levels that would be consistent with acute myocardial infarction in the general population (>0.1 μg/L).[196] However, these small elevations in cardiac markers do have prognostic importance. Chronic elevation of troponin T predicts mortality in both stages 3 and 4 CKD and dialysis patients, identifying patients with greater left ventricular dilatation and impaired left ventricular systolic and diastolic function,[93,197–199] whereas elevations in NT-proBNP and BNP predict underlying IHD and hypertrophy independent of level of kidney function and are also associated with mortality.[93]

Accordingly, although any elevation in these cardiac markers may identify increased chronic risk, in the absence of a suggestive electrocardiogram for AMI, diagnosis of AMI may be best accomplished by following the trend of levels of troponin and other cardiac injury markers, as a sequential rise and fall in levels of these markers is consistent with acute cardiac damage.[200]

Prevention and Treatment

In dialysis patients, to date there are no large randomized clinical trials demonstrating a significant survival benefit with any accepted coronary therapies, leaving current practice decisions dependent on observational data and extrapolations from the non-CKD population. Even risk factor management remains uncertain, reflecting the lack of medical evidence, difficulties of balancing blood pressure control with the risk of hypotension, tempering a healthy diet with the risk of malnutrition in the catabolic dialysis milieu, and the challenge of even adequately assessing risk. With little definitive supporting evidence, opinion-based clinical practice guidelines extrapolating data from the nondialysis population have recommended the following targets: (1) predialysis blood pressure goal of >140/90 mmHg while avoiding orthostatic and intradialytic hypotension; (2) serum LDL cholesterol less than 100 mg/dl in individuals with

known atherogenic disease; and (3) reasonably tight diabetes control based on frequent glucose assessments. Blood pressure control may be optimally accomplished by achieving appropriate dry weight followed by pharmacological therapy, with opinion favoring the use of ACE inhibitors or ARBs potentially reflected in a positive trend among a subgroup of dialysis patients with hypertension randomized to fosinopril versus placebo.[201] Finally, smoking cessation efforts are essential in all stages of CKD.

For primary treatment of IHD in dialysis patients, older observational data predating the use of drug-eluting stents suggested a long-term benefit to bypass grafting;[88] however, there are no trial data demonstrating superiority among any of medical management, bypass grafting, or angioplasty with stenting. Whether this paucity of data has caused or is a consequence of a degree of therapeutic nihilism prevalent in the cardiac care of patients with advanced CKD is uncertain, but it in part reflects the fact that there are numerous competing causes of death in these patients, and addressing only one at a time may not make a significant impact in reducing mortality.

For individuals with stages 3 or 4 CKD, therapeutic data, particularly data evaluating primary prevention, are lacking, predominantly reflecting the fact that many studies have excluded participants with elevated serum creatinine.[202] Therefore, we rely on posthoc subgroup analyses derived from larger clinical trials that often excluded individuals with serum creatinine above 2 or 3 mg/dl. In general, most of these studies demonstrate benefits for stage 3 to 4 CKD patients that are similar to those appreciated in the general population, and treatment strategies for primary prevention of cardiac disease in individuals with CKD mirror those seen in the general population.[75,79,91] For example, in a subset of the HOPE trial examining patients with stage 3 to 4 CKD and at least one other CVD risk factor, ACE inhibitor therapy reduced negative cardiovascular outcomes.[21] Notably, there are challenges specific to the CKD population, including more frequent hyperkalemia with blockade of the renin-angiotensin-aldosterone system and an increased risk of rhabdomyolysis seen with dual statin and fibrate therapy (a combination that should be avoided in advanced CKD).

Among individuals with stage 3 to 4 CKD and those receiving dialysis, there are minimal trial data on secondary prevention strategies in CKD; however, in the absence of active or chronic gastrointestinal bleeding, there is no specific contraindication to chronic antiplatelet therapy with aspirin or clopidogrel. Observational data are extensive, with studies demonstrating that beta blockers, ACE inhibitors, and aspirin are beneficial in patients with stages 3 to 5 CKD and IHD.[8,9,203–205] Similarly, in an observational study of patients with stages 3 to 5 CKD and AMI, significantly improved survival was noted in adjusted analysis for those treated with angioplasty versus bypass surgery. Additionally, patients receiving either, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) did better than those who only were managed medically.[206] However, it remains difficult to draw treatment conclusions based on the observational data available. Perhaps reflecting this lack of trial data, it has been shown that individuals with CKD are less likely to receive revascularization therapies, such as coronary artery bypass grafting and percutaneous angioplasty with stenting, and typically appropriate medications following AMI, including aspirin, beta-blocking agents, ACE inhibitors, and lipid-lowering agents.[41,207]

Heart Failure

Heart failure is generally characterized by volume overload, pulmonary edema, and dyspnea. Heart failure may occur as a result of either left ventricular systolic dysfunction or diastolic dysfunction in which the left ventricle has a normal ejection fraction but impaired filling.

Epidemiology

Both prevalent and incident heart failure are common in CKD. For incident heart failure, in the ARIC study of individuals aged 45 to 64 years, those with an eGFR less than 60 ml/min/1.73 m^2 at baseline had twice the risk of hospitalization for heart failure and death compared to participants with an eGFR of at least 90 ml/min/1.73 m^2, regardless of the presence of baseline coronary disease.[208] Similarly, in a population of 60,000 insured individuals in northern California with prevalent chronic heart failure, 24% had an eGFR of 45 to 59 ml/min/1.73 m^2, 11% had an eGFR of 30 to 44 ml/min/1.73 m^2, and 4% had an eGFR less than 30 ml/min/1.73 m^2 (not receiving dialysis).[209] The high incidence and prevalence of heart failure extends to the dialysis population, where approximately 25% of hemodialysis and 18% of peritoneal dialysis patients in the United States will be diagnosed with heart failure annually, and approximately 55% of prevalent hemodialysis patients are identified as having a history of heart failure.[210]

Diagnosis

Although heart failure is a clinical diagnosis, echocardiography is a safe, accurate, and readily available tool for assessment of cardiac structure and function. However, several factors particular to dialysis patients may affect the accuracy of echocardiography; specifically, as discussed in the section on LVH, assessment of left ventricular mass may be confounded by volume status and timing of dialysis.[211–213] Several newer biomarkers, notably brain natriuretic peptides, correlate with left ventricular ejection fraction, can be useful for the diagnosis of acute heart failure in stage 3 CKD, and are associated with future CVD events in all CKD stages.[214,215] However, with regard to these brain natriuretic peptides, there are no current data to support their measurement in guiding treatment decisions.[216]

Treatment

Acute heart failure therapy differs by CKD stage; diuretics are a mainstay of therapy in predialysis patients, whereas acute fluid overload in dialysis patients is treated with ultrafiltration. Limited data exist regarding CKD-specific chronic treatment of heart failure, but, for earlier stages of CKD, posthoc analyses of clinical trials suggest that most interventions in the general population also apply. For example, two randomized, placebo-controlled trials studying individuals with diabetes and proteinuric stage 3 to 4 CKD have established a role for ARBs in reducing the risk of developing heart failure; however these studies failed to show a benefit in cardiovascular or all-cause mortality, probably reflecting insufficient power to evaluate these secondary outcomes.[60,64] Theoretically, further benefits may be associated with aldosterone blockade, although the use of medications like

spironolactone may be limited by hyperkalemia, especially when used in conjunction with ACE inhibitors or ARBs. Beta-blocking agents, another mainstay of heart failure therapy in the general population, also appear beneficial in patients with CKD, with evidence supporting carvedilol use to reduce mortality risk in dialysis patients with left ventricular dysfunction.[204] Cardiac glycosides (e.g., digoxin) are frequently used for heart failure in the general population where they decrease morbidity but not mortality.[217] Although there are no specific studies of cardiac glycosides in CKD, they should be used extremely judiciously, with careful attention to dosage, drug levels, and potassium balance.

STRUCTURAL DISEASE: PERCARDIAL AND VALVULAR CONDITIONS

Pericardial Disease

Pericardial disease in CKD is generally associated with stage 5 CKD. It most commonly manifests as acute uremic or dialysis-associated pericarditis although chronic constrictive pericarditis may also be seen (Table 10-7). Uremic pericarditis describes patients who develop clinical manifestations of pericarditis prior to or within 8 weeks of initiation of kidney replacement therapy. With the advent of modern dialysis, uremic pericarditis is exceedingly rare but remains an indication for and responds extremely well to initiation of dialysis.[218] Dialysis-associated pericarditis by definition occurs after a patient is stabilized on dialysis. The precise etiology is unknown but may be related to inadequate dialysis and volume overload.

Pericarditis may be accompanied by nonspecific symptoms including chest pain, fever, chills, malaise, dyspnea, and cough. Physical examination may reveal a pericardial friction rub. When hemodynamically significant, pericardial disease accompanied by an effusion may be characterized by hypotension, particularly during the hemodialysis procedure.[219] Although other expected signs of pericardial effusion may be present, dialysis-related pericarditis often does not manifest with the classical electrocardiogram finding of diffuse ST segment elevation because there may be only minimal inflammation of the epicardium.[220] Echocardiography is helpful to diagnosis pericarditis in dialysis patients; however, effusions may be absent in patients who have adhesive, noneffusive pericarditis.

Treatment is dependant upon symptoms and effusion size. Small, asymptomatic pericardial effusions are fairly common in dialysis patients and require no acute intervention, whereas larger effusions present a risk for tamponade. Intensification of hemodialysis is the mainstay of therapy but is only effective approximately 50% of the time.[218] Traditionally, heparin has been avoided during dialysis out of concern for hemorrhagic tamponade. Adjuvant medical therapies, including oral and intravenous glucocorticoids and nonsteroidal antiinflammatory medications, have generally not been effective. For patients with hemodynamic instability, treatment consists of emergent drainage of the pericardial effusion. This is generally accomplished by pericardiocentesis or pericardiotomy with or without pericardiostomy for the instillation of long-acting, nonabsorbable glucocorticoids.[221]

Endocarditis

Infective endocarditis is a relatively common complication of hemodialysis,[222] which reflects the relatively high incidence of bacteremia, chronic use of dialysis catheters, and the high prevalence of preexisting valvular abnormalities.[223–225] The majority of endocarditis in hemodialysis patients is secondary to gram-positive organisms, with *Staphylococcus aureus* predominating.[226–228] Dialysis patients with endocarditis usually have fever; murmurs, leukocytosis, and septic emboli may also be common. The mitral valve is the most commonly affected, followed by the aortic valve.[226–228] Diagnosis is chiefly dependent on positive blood cultures and clinical suspicion; clinical suspicion should be high in settings where bacteremia is persistent and in individuals with prior history of endocarditis. Transthoracic and transesophageal echocardiography are important in establishing the diagnosis.

TABLE 10-7 Structural CVD and Rhythm Disorders Common in Individuals with CKD

TYPE OF CVD	CONDITION	RISK FACTORS	DIAGNOSIS	CLINICAL SEQUELAE
Structural disease	Pericardial disease	Delayed or insufficient dialysis	Physical examination, echocardiography	Heart failure, hypotension
	Valvular disease	CKD-MBD, aging	Physical examination, echocardiography	Aortic stenosis, endocarditis, heart failure
	Mitral annular calcification	CKD-MBD	Echocardiography reveals uniform echodense rigid band located near the base of the posterior mitral leaflet	Arrhythmia, embolism, endocarditis, heart failure
	Endocarditis	Valvular disease, chronic venous catheters	Echocardiography, physical examination	Arrhythmia, heart failure, embolism, sepsis
Arrhythmia	Atrial fibrillation	Ischemic heart disease, cardiomyopathy, volume overload	Electrocardiography	Hypotension, embolism
	Ventricular arrhythmia	Ischemic heart disease, cardiomyopathy, electrolyte abnormalities	Electrocardiography, electrophysiology study	Sudden cardiac death

CKD-MBD, chronic kidney disease-mineral bone disorder.

Treatment of endocarditis begins with appropriate antibiotic therapy, but even with appropriate therapy, survival is often poor, with case series showing 30% mortality during the initial hospitalization and 1-year mortality over 50%.[226–229] Surgical intervention may also be appropriate, and indications for surgery are the same as in the general population: progressive valvular destruction, progressive heart failure, recurrent systemic emboli, and failure to respond to appropriate antibiotic therapy. Factors associated with mortality include hypoalbuminemia, involvement of multiple valves, and severe valvular insufficiency. In one study, 30-day survival among patients who had surgery was 80%, whereas it was only 47% among those managed medically.[227] Although current data are observational, an important inference to be made is that hemodialysis patients with endocarditis should be considered surgical candidates if they have indications.

Mitral Annular Calcification

Mitral annular calcification may occur in 30% to 50% of patients on dialysis and is also common in patients during the earlier stages of CKD.[230,231] It is recognized on echocardiography as a uniform echodense rigid band located near the base of the posterior mitral leaflet and may progressively involve the posterior leaflet. The pathogenesis of mitral calcification may be linked to altered mineral metabolism.[231,232] Serious complications of mitral annular calcification include conduction abnormalities, embolic phenomena, mitral valve disease, and an increased risk of endocarditis.[233]

Aortic Calcification and Stenosis

Aortic valve calcification is common in dialysis patients, occurring in 28% to 55% of patients. Although the overall prevalence is similar to that seen in the general population, dialysis patients experience aortic valve calcification 10 to 20 years earlier than the general population.[234] Age is the most significant risk factor for aortic valve calcification,[233] and abnormal mineral metabolism may also play a role.[235]

The most significant hazard associated with aortic valve calcification is the potential for the development of progressive immobilization of the aortic leaflets, which eventually restricts flow. Aortic stenosis occurs when the valve leaflets thicken to the extent that commissural fusion can no longer occur and a pressure gradient develops across the aortic valve. In one study of dialysis patients, the estimated incidence of symptomatic aortic stenosis was 3.3% per year.[235] Progression of aortic valve calcification to aortic stenosis in dialysis patients appears more rapid than that in the general population.[236] Very little evidence exists in the nondialysis CKD population as to the prevalence and progression of valvular abnormalities.

Angina, heart failure, and syncope are the cardinal symptoms of critical aortic stenosis. Clinical evidence of aortic stenosis may be more readily evident in dialysis patients as they may have more frequent episodes of intradialytic hypotension, particularly as ultrafiltration can rapidly reduce preload.

Treatment of aortic stenosis is multifaceted, encompassing prevention of progression, prevention of endocarditis, and eventual repair of the valve. Management of mineral metabolism abnormalities could theoretically slow progression of aortic stenosis, although this has not been proven. Valve replacement is the therapy of choice for critical aortic stenosis, and the timing of surgery is dependant on individual patient characteristics with the caveat that surgery should be performed before left ventricular contractility becomes diminished. There currently is no consensus for a benefit of either prosthetic versus bioprosthetic valves in dialysis patients.[237] Dialysis patients undergoing valve replacement have a high mortality rate—17% operative mortality for aortic valve replacement in dialysis patients, 23% for mitral valve replacement, 25% for aortic valve replacement and CABG, and 37% for mitral valve replacement and CABG.[238] However, in most cases the prognosis is worse if clinically indicated surgery is not performed or if emergent rather than elective surgery is performed.[230]

ARRHYTHMIA AND SUDDEN CARDIAC DEATH

Patients with CKD are at high risk for arrhythmia due to a high prevalence of structural heart disease (including cardiomyopathy, mitral annular calcification, and other valvular disease), heart failure, and coronary disease. Hemodialysis patients are also exposed to rapid shifts in ions, including potassium, calcium, hydrogen, and magnesium.

Atrial Fibrillation

Both atrial and ventricular arrhythmias are common in dialysis patients. Mirroring the general population, atrial fibrillation is the most common of these arrhythmias, with an annual incidence of over 10%.[239] In the USRDS DMMS Wave 2 cohort, 123 out of 3374 patients (3.6%) were hospitalized with a primary diagnosis of atrial fibrillation (12.5 hospitalizations per 1,000 person years).[240]

The major complications of atrial fibrillation include loss of the "atrial kick" and cardiac synchronicity leading to diminished cardiac function and occurrence of thromboembolic phenomena. Very little data exist as to how common thromboembolism is in dialysis patients with atrial fibrillation. Optimal management involves rate control with or without restoration of sinus rhythm, although patients with symptoms may benefit from a return to sinus rhythm.[241–243] Beta blockers and calcium channel blockers are useful for rate control, whereas amiodarone is useful for both slowing the rate and for chemical cardioversion. Anticoagulation with warfarin has not been prospectively studied in dialysis patients, although analysis of the DMMS Wave 2 database showed a survival benefit for patients who were on warfarin at the time of hospitalization for atrial fibrillation.[240] At this time, the benefits and risks of anticoagulation in dialysis patients should be considered on an individual patient basis.

Ventricular Arrhythmias and Sudden Death

Ventricular arrhythmias and ectopy are also common in CKD. There are currently no data indicating that cardiac management of patients prone to arrhythmia should be any different than in the general population.

Identified arrhythmias and cardiac arrest of unknown cause account for 60% of cardiac deaths in dialysis patients.[1] During the first year of dialysis, the rate of cardiac arrest is 93 events per 1,000 patient years; this nearly doubles by the fourth year of dialysis such that 43% of dialysis patients have had cardiac arrest by this time. Thirty-day survival after cardiac arrest is only 32% and 1-year survival is 15%.

Potential strategies to reduce the risk of fatal cardiac arrhythmias include careful attention to fluid and electrolyte shifts. Hemodialysis units may benefit from the presence of and training in the use of automated external defibrillators. Other potential interventions may include routine use of beta blockers, although this has not been investigated. Finally, studies of the appropriate use of implantable defibrillators in dialysis patients are needed.

A full list of references are available at www.expertconsult.com.

Chapter 11

COMPLICATIONS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE: DIABETES

Katherine R. Tuttle, M.D., F.A.S.N., F.A.C.P.

WHY DIABETES AND CHRONIC KIDNEY DISEASE MATTER: A PARADIGM OF COMPETING RISKS

Vascular complications are the major causes of death and disability in people with diabetes. These complications are customarily divided into micro- and macrovascular categories. Although this categorization is conceptually expedient, there is a great deal of overlap, especially as related to amplification of diabetes risks. Among the microvascular complications (retinopathy, neuropathy, and nephropathy), diabetic kidney disease (DKD) is one of the most common, occurring in about 30% of those with types 1 diabetes and about 40% in type 2 diabetes.[1] DKD trends are evolving depending on the population and treatment strategies. Based on long-term epidemiological studies in the United States and Europe, the incidence of end-stage renal disease (ESRD) in type 1 diabetes has been steadily lessening over the past 40 years.[2,3] This trend has been ascribed to progressive improvements in overall diabetes care. In contrast, ESRD due to DKD is on the rise in other populations, particularly those with type 2 diabetes who may be less likely to access advantageous diabetes care, like young Native Americans and African Americans (Figure 11-1).[4,5] Moreover, there has been a troublesome increase in type 2 diabetes incidence, which is a prerequisite for developing DKD, among the young in these ethnic groups (Figure 11-2).[6] Knowledge of such trends is essential in order to efficiently allocate resources to high-risk groups.

Within the field of nephrology, the principal concern about DKD has traditionally been progression to ESRD. This concern is certainly well-founded considering that DKD, with the most recent annual incidence rate of 54% in the United States, dwarfs other causes of ESRD in the developed world (see Figure 11-2).[4] Recent data from the United States Renal Data System suggest that the overall rate of ESRD due to DKD may be stabilizing.[4] However, the total burden of diabetes remains great in ESRD with a frequency of 66% to 86% in prevalent patients depending on race (higher in nonwhite populations).[4] Yet more sobering, people with diabetes and chronic kidney disease (CKD) are more likely to die than reach ESRD primarily due to the effect of kidney disease to amplify mortality from all causes, especially cardiovascular disease (CVD).[4] The United Kingdom Prospective Diabetes Study (UKPDS) showed that once patients with diabetes develop macroalbuminuria, death rates outpace CKD progression by about 2:1 (Figure 11-3).[7] By the time glomerular filtration rate (GFR) falls, the death rate approaches 20% per year.[7] Excess CVD risk in patients with type 1 diabetes was at least partly attributable to

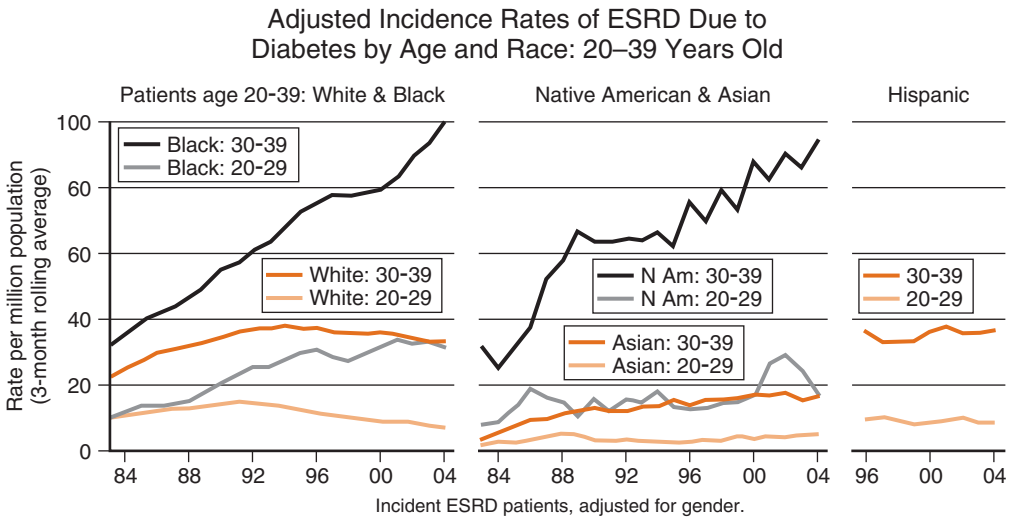


FIGURE 11-1 Adjusted incidence rates of ESRD due to diabetes by race for the 20- to 39 year-old age group in the United States for the year 2006. (Data from U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009.) In 2010, the American Diabetes Association added a hemoglobin A1c (HbA1c) level >6.5% to the diagnostic criteria for diabetes. Importantly, a positive test for diabetes should be repeated on a separate occasion to confirm the diagnosis.[9]

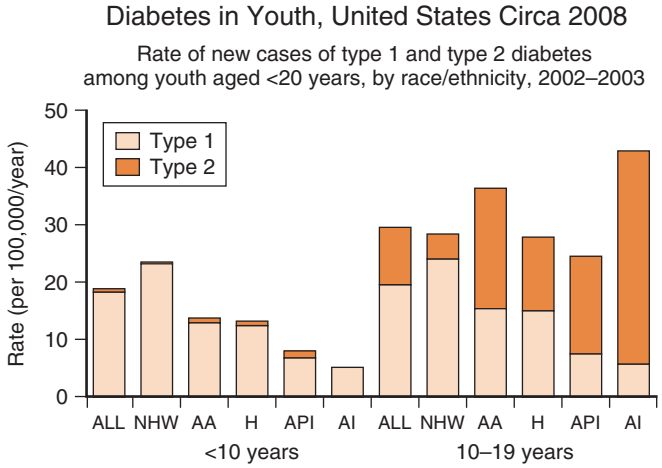


FIGURE 11-2 Incidence rates of new-onset type I and type 2 diabetes among youth younger than 20 years by race for the years 2002 to 2003. *NHW,* Non-Hispanic white; *AA,* African American; *H,* Hispanic; *API,* Asian Pacific Islander; *AI,* American Indian. (Data from Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.)

underlying kidney disease in the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, thereby identifying patients with DKD as a subset at particularly high risk.[8] Strategies to reduce mortality and CVD risk in DKD must be elevated to top priority along with efforts to prevent or slow progression to ESRD.

The scope of this chapter will be primarily devoted to management of diabetes in the setting of CKD, either due to DKD or other causes, and emerging issues in diabetes and CKD. Three major related topics are covered in other chapters of this textbook: First, assessment and treatment of DKD, per se, is reviewed in Chapter 3. Second, the general approach to CVD in CKD is addressed in Chapter 10. Third, kidney replacement therapies (hemodialysis, peritoneal dialysis, transplant) are discussed in a series of chapters (20 through 44).

MANAGEMENT OF DIABETES IN THE SETTING OF CHRONIC KIDNEY DISEASE: WHAT IS THE SAME AND WHAT IS DIFFERENT?

Hyperglycemia and General Diabetes Care

Treatment of Hyperglycemia

Diabetes is defined by the condition of hyperglycemia, a fasting blood glucose level greater than or equal to 126 mg/dl, or a casual (random) or 2-hour, post-75 gm glucose load level of blood glucose greater than or equal to 200 mg/dl.[9] Most recently, the American Diabetes Association (ADA) has also endorsed a hemoglobin A1c (HbA1c) level >6.5% as diagnostic for diabetes. If a diagnostic test is positive, it should be repeated on a separate occasion to confirm the diagnosis of diabetes. The goal of reducing blood glucose is to avoid complications of severe hyperglycemia (ketoacidosis and hyperosmolar state) in the short-term and to prevent development and progression of complications in the long-term. The effect of intensive glycemic control to decrease risk of microvascular disease is well-established in types 1 and 2 diabetes.[10–14] On the other hand, effects of intensive glycemic control on macrovascular disease are less certain, particularly in type 2 diabetes (see *Controversies* section).

The ADA Standards of Medical Care in Diabetes recommend a HbA1c goal less than 7% for most people with diabetes (Table 11-1).[9] The Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease from the National Kidney Foundation (NKF)—Kidney Disease Outcomes Quality Initiative (KDOQI) have endorsed this recommendation for patients with diabetes who also have CKD.[1] For these patients, the goal of treating hyperglycemia is not only for its impact on kidney disease, but also for other microvascular complications. Importantly, reporting for HbA1c now includes an "estimated average glucose" level as part of international

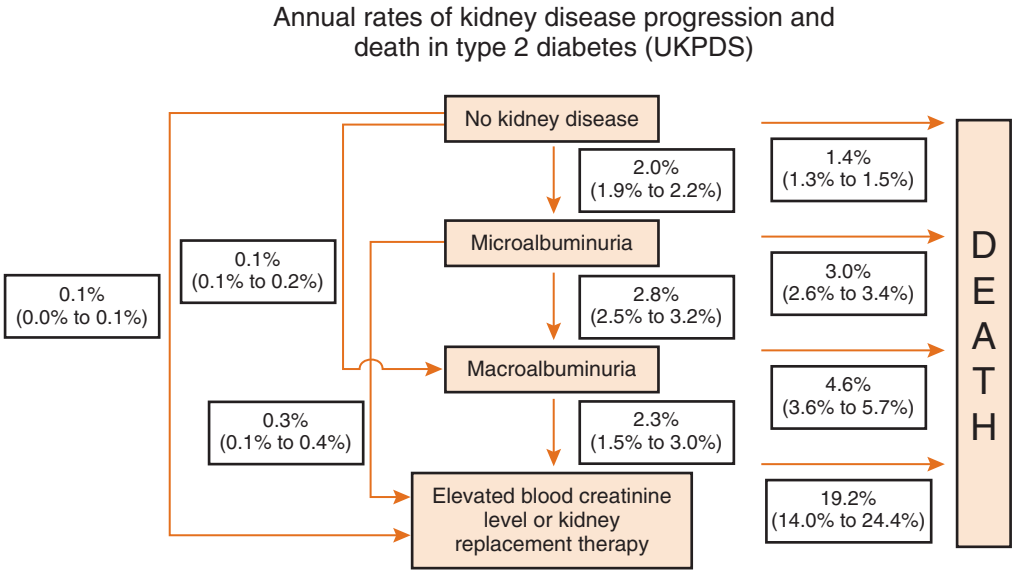


FIGURE 11-3 Annual rates of kidney disease progression and death in type 2 diabetes among participants in the United Kingdom Prospective Diabetes Study. (Adapted from Adler A, Stevens R, Manley S, et al. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003; 63:225–232.)

TABLE 11-1 ADA Recommendations for Glycemic Control Assessment and Goals[9]

MEASUREMENT	FREQUENCY	GOAL
HbA1c	Twice per year in stable patients who are achieving goals Every 3 months after change in treatment or if goal not achieved	<7.0% (Generally)
Pre-prandial capillary glucose by SMBG	3 or more times daily if treated with multiple insulin injections Daily or sufficiently often to achieve goals if treated with fewer insulin injections, oral agents, or medical nutrition therapy	70-130 mg/dl (3.9-7.2 mmol/l)
Peak postprandial capillary glucose by SMBG (1-2 hours after beginning a meal)	As needed May be particularly helpful in patients with gastroparesis	<180 mg/dl (<10.0 mmol/l)

(Adapted from American Diabetes Association: Standards of medical care in diabetes—2009. Diabetes Care 2009; 32:S13–S61.)
SMBG, self-monitoring of blood glucose

standardization of assays. However, patients with kidney disease or anemia were not included in the validation study, which makes estimated average glucose less reliable in patients with diabetes and CKD.[15]

Drug Therapy

The primary goal of drug therapy is to lower blood glucose to a range associated with reduced risk of microvascular complications without excessive episodes of hypoglycemia. In type 1 diabetes, insulin replacement remains the primary approach, although adjunctive agents (e.g., amylin analog) may be added in some cases. There is no single "preferred" drug class for treatment of hyperglycemia in type 2 diabetes, and most classes can be used in patients with CKD. However, some drugs have limitations on use due to safety concerns or necessary dosage adjustments in the setting of CKD. The most common precaution for drugs used to treat hyperglycemia is increased risk of hypoglycemia due to decreased clearance, drug interactions, and impaired kidney gluconeogenesis. Risk of hypoglycemia can usually be managed by reducing dosages or using agents within a particular class that are preferred because dosage adjustment is not required for decreased kidney function (Tables 11-2 and 11-3).[1,9]

Insulin and Insulin Secretagogues

It is important to recognize that insulin requirements generally decrease as kidney function declines.[16–19] Insulin doses must be carefully adjusted based on individual sensitivity to glucose lowering, severity and frequency of hypoglycemia, and other comorbidities that increase hypoglycemic risk (e.g., congestive heart failure, chronic liver disease, and malnutrition). Among the sulfonylurea class of insulin secretagogues, glipizide is the preferred agent because dosage adjustment is not required in the setting of CKD.[20–22] For similar reasons, repaglinide is preferred among the mitiglinide class of insulin secretagogues.[23–25]

Metformin—Prototype for the Biguanide Class of Insulin Sensitizers

The insulin-sensitizing agent, metformin, has one of the most important safety precautions for patients with CKD. In patients with reduced kidney function, the risk of lactic acidosis is increased.[26,27] Although this side effect is rare (about 0.03 cases per 1000 patient-years), about half of lactic acidosis cases are fatal. Therefore, the United States Food and Drug Administration (FDA) labeling for metformin indicates that this drug should not be used in men with serum creatinine levels above 1.5 mg/dl or women with serum creatinine levels above 1.4 mg/dl. Even though serum creatinine levels do not consistently correlate with estimated GFR (eGFR) across populations, the KDOQI guidelines and recommendations remain based on serum creatinine due to FDA labeling in this particular circumstance.[1]

TABLE 11-2 Dosing Adjustments by CKD Stage for Drugs Used To Treat Hyperglycemia

CLASS	DRUG	DOSING RECOMMENDATION FOR CKD STAGES 3, 4, OR KIDNEY TRANSPLANT	DOSING RECOMMENDATION FOR DIALYSIS
Sulfonylureas	Acetohexamide	Avoid	Avoid
First generation	Chlorpropamide	Reduce dose by 50% when eGFR <70 and >50 ml/min/1.73 m^2 Avoid when eGFR <50 ml/min/1.73 m^2	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second generation	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in United States	Preferred sulfonylurea No dose adjustment necessary Not available in United States
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-Glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dl	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dl	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dl in men or ≥1.4 mg/dl in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 0.5 mg before each meal	Avoid
Thiazolidine-diones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin therapies	Exenatide	No dose adjustment necessary	No dose adjustment necessary
	Sitagliptin	Reduce dose to 50 mg/day orally when eGFR <50 and >30 ml/min/1.73 m^2 and 25 mg/day orally when eGFR <30 mL/min/1.73 m^2	Reduce dose to 25 mg/day orally
Amylin analog	Pramlintide	No dose adjustment necessary for eGFR 20-50 ml/min per 1.73 m^2	No data available

(Adapted from National Kidney Foundation—Kidney Disease Outcomes Quality Initiative [NKF-KDOQI], Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease, Am. J. Kidney Dis. 49 [2007] S1–S179.)
eGFR, estimated glomerular filtration rate; *SCr*, serum creatinine.

TABLE 11-3 Clinically Relevant Interactions with Drugs Used To Treat Hyperglycemia

CLASS	DRUG	INTERACTION	MANAGING THE INTERACTION
Meglitinides	Repaglinide	Gemfibrozil increases repaglinide concentrations and half-life. Inhibitors of CYP 3A4 system	Combining repaglinide and gemfibrozil is not recommended. If clinically necessary, reduce the dose of repaglinide and monitor blood glucose carefully to avoid hypoglycemia
	Nateglinide	Nateglinide inhibits CYP 2C9	Initiate doses of 2C9 substrates (e.g., amiodarone, fluoxetine, phenytoin and warfarin) at lower doses and monitor carefully
Thiazolidinediones	Pioglitazone	Pioglitazone may interact with CYP 3A4 inducers or inhibitors	If combined use of pioglitazone with a CYP 3A4 inducer is necessary, consider reducing dose of pioglitazone and careful blood glucose monitoring to avoid hypoglycemia
	Rosiglitazone	Gemfibrozil increases rosiglitazone area under the curve and half-life by inhibiting CYP 2C8	If combination treatment with gemfibrozil and rosiglitazone is necessary, decrease rosiglitazone dose by 50% to 70% and monitor blood glucose carefully to avoid hypoglycemia

(Adapted from National Kidney Foundation—Kidney Disease Outcomes Quality Initiative [NKF-KDOQI], Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease, Am. J. Kidney Dis. 49 [2007] S1–S179.)

Thiazolidinediones Class of Insulin Sensitizers

The thiazolidinedione (TZD) class of drugs does not require dosage adjustment for reduced kidney function, but caution is in order due to the high frequency of fluid retention that may be especially problematic for patients prone to edema (e.g., nephrotic syndrome, advanced CKD, or congestive heart failure). In fact, the American Heart Association and the ADA have jointly recommended that the TZD class be avoided in those with New York Heart Association class III or IV congestive heart failure.[28] In those with less severe heart failure, TZD drugs should be administered cautiously with initiation of treatment at the lowest dose and gradual dose escalation. More time than usual should be allowed to reach the target for glycemic control when a TZD drug is used in patients with edema. In addition, a TZD, rosiglitazone, has been associated with higher risk of myocardial infarction (MI), hospitalization for heart failure, and all-cause death and possibly CVD-related death.[29,30] Nevertheless, rosiglitazone currently remains on the market in the United States. Increased risks of death and CVD have not been reported for pioglitazone, but this evidence must be carefully reexamined as data accumulate. Safety issues have beset the TZD drug class since the early clinical experience

with these agents. Indeed, the first TZD approved by the United States FDA, troglitazone, was soon removed from the market due to increased risk of fatal liver failure.[31]

Acarbose—Prototype of Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibition works by reducing glucose absorption due to decreased carbohydrate digestion. Although acarbose can be used as monotherapy, it is typically added to insulin or other oral agents to achieve glycemic control in type 2 diabetes.[27] To mitigate the primary side effect of gastrointestinal upset (flatulence, diarrhea, pain), dosage should be increased gradually. Acarbose acts locally in the gastrointestinal tract, but absorbed metabolites that are normally excreted by the kidney accumulate in patients with reduced GFR.[1] Therefore, acarbose should be avoided in patients with stage 4 to 5 CKD.

Incretin Therapies and Amylin Analog

The incretin therapies and an amylin analog are recently available agents to enter the clinical realm for treatment of hyperglycemia. Several members of these classes are currently FDA-approved for use in the United States: an analog (pramlintide) of amylin, a hormone normally cosecreted with insulin by pancreatic beta cells; an analog (exenatide) of glucagon like-peptide-1 (GLP-1), a hormone normally released from small bowel L cells; and a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin) that prevents inactivation of GLP-1 and gastrointestinal peptide (GIP).[32,33] The incretin therapies (GLP-1 analog and DPP-4 inhibitor) raise GLP-1 and predominantly work by enhancing pancreatic insulin secretion in response to nutrients and glucose in the gut. Pramlintide (amylin analog) and the incretin therapies slow gastric emptying, reduce glucagon secretion, and suppress appetite. As such, the incretin therapies are only useful in management of type 2 diabetes. Although pramlintide may be administered to patients with either type I or type 2 diabetes, it is most commonly applied to management of type 2 diabetes (Figure 11-4).

An important advantage of the incretin therapies and the amylin analog is that these agents are not associated with weight gain, in contrast to most other types of treatment for hyperglycemia. Moreover, analogs of amylin and GLP-1 are typically associated with modest weight loss (2 to 5 kg) that appears to be dose-dependent and progressive.[32] Because the risk of hypoglycemia is increased with the use of combination glucose-lowering treatments, doses of insulin or oral agents should be reduced when initiating incretin therapies or the amylin analog. Pramlintide is approved by the FDA for use in insulin-treated patients. On the other hand, exenatide is approved for use with oral hypoglycemic agents, but not as monotherapy or in combination with insulin. The most frequent side effects of pramlintide and exenatide are nausea and delayed gastric emptying.[32,33] These drugs should be avoided in patients with gastroparesis because they may exacerbate symptoms and may delay absorption of orally administered medicines. Although doses of pramlintide and exenatide do not require dosage adjustment in CKD, these agents should be administered cautiously (e.g., slow dose titration) to reduce risk of hypoglycemia in patients with CKD stage 4 or kidney transplant, and they should be avoided in patients treated by dialysis.[1] Both pramlintide and exenatide must be administered by subcutaneous injection. In contrast, sitagliptin is an oral agent that is approved for use as either monotherapy or in combination with metformin, sulfonylureas, or TZDs. The DPP-4 inhibitor appears less likely to cause gastrointestinal side effects than exenatide.[32,33] Doses of sitagliptin should be reduced for decreased kidney function (see Table 11-2).

Therapeutic Lifestyle Changes

Carbohydrate Intake

Intake of carbohydrates must be addressed in a holistic approach to dietary management, particularly if fats and protein are also adjusted in the setting of diabetes and CKD. Evidence regarding specific effects of carbohydrate moieties on kidney disease is scant, but carbohydrate intake is relevant

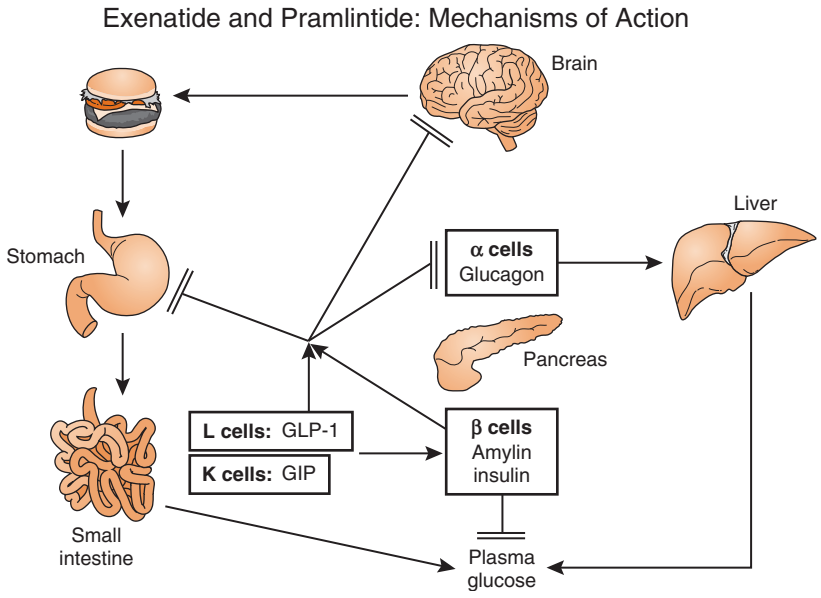


FIGURE 11-4 Sites and mechanisms of action for the incretin therapies and amylin analog. *Arrows* indicate stimulation. *Double bars* indicate inhibition.

because of its impact on glycemia and lipids, which are key risk factors for CKD and CVD. According to the National Academy of Sciences, Institute of Medicine, nonprotein calories should be distributed as up to 60% obtained from complex carbohydrates and 30% or less from dietary fats.[34] Phosphate binders may be needed earlier in the course of CKD if foods with higher phosphorous content, such as grains and dairy products, are encouraged to curtail meat consumption.

From the perspective of managing hyperglycemia, the ADA recommends that carbohydrates be derived primarily from whole grains, fruits and vegetables, and nonfat or low-fat dairy products.[9] Effects on glycemia are principally determined by total carbohydrate content. Additionally, low glycemic index foods (determined by carbohydrate type) can be recommended because they provide an incremental benefit beyond carbohydrate counting alone.[9] Dietary fiber is encouraged and appears to produce metabolic benefits on glycemia and lipids.[9]

Weight Control and Exercise

To introduce this concept, a few words about the Diabetes Prevention Program are in order. This landmark clinical trial clearly demonstrated that diabetes can be effectively prevented by a lifestyle intervention characterized by modest weight loss (5% to 10% of body weight) and 150 minutes per week of moderate exercise (e.g., brisk walking) in overweight or obese people with impaired glucose tolerance.[35] As expected, indices of glycemia were significantly reduced by this lifestyle intervention. Results of the Diabetes Prevention Program have now been confirmed by subsequent studies across the globe from Europe to Asia.[36–38] Long-term follow-up for as long as 20 years after the start of lifestyle intervention has demonstrated that the effect on diabetes prevention can be sustained.[36,37] These studies address the fundamental driving force behind the diabetes epidemic, which is lifestyle—how people live. Most importantly, prevention of diabetes, which inherently means preventing hyperglycemia, is paramount to reducing the incidence of diabetic complications. Although the existing clinical trials have insufficient data to prove an effect on reducing risk of micro- or macrovascular complications, weight management and exercise should still receive attention for optimal control of hyperglycemia and other risk factors for CKD and CVD.[35–38]

Fatness is a driving force behind DKD and its major complications, notably, death and ESRD.[39–42] The World Health Organization has defined overweight as a body mass index (BMI) greater than or equal to 25 kg/m^2 and provided specific criteria for obesity stages I (BMI 30 to 34.9 kg/m^2), II (BMI 35 to 39.9 kg/m^2), and III (BMI greater than 40 kg/m^2).[43] A recent metaanalysis reported that 24% and 34% of overall kidney disease among men and women, respectively, is attributable to overweight and obesity in the United States.[40] Additionally, overweight and obesity have been associated with excess deaths due to diabetes and kidney disease in a population-based study in the United States.[39] Waist circumference correlates with abdominal fat and may outperform BMI for prediction of cardiovascular events in CKD, which is the most common cause of death in this setting.[44] Moreover, the influence of corpulence extends to an antecedent of kidney disease, as reflected in increased risk of elevated cystatin C (a marker associated with early loss of kidney function) with increasing BMI categories.[41] Although these effects are mediated by development of diabetes and hypertension to a large extent, nutrient overfeeding and increased fat mass may independently promote kidney disease.[45]

Weight loss and adjustment of nutrient intake are established tactics to improve hyperglycemia.[46,47] Moreover, weight loss may ameliorate kidney disease progression, as reflected in reduced proteinuria in both diabetic and nondiabetic kidney diseases.[48] Weight goals have been addressed in the KDOQI Clinical Practice Recommendations section for Diabetes and Chronic Kidney Disease.[1] Although these recommendations suggest that patients with diabetes and CKD should aim for a "normal" BMI in the range of 18.5 to 24.9 kg/m^2, this was primarily based on extrapolation. Thus, KDOQI and others have encouraged research to develop data-driven BMI targets for patients with diabetes and CKD.[1,49]

The American College of Physicians guidelines for obesity state that patients with a BMI greater than or equal to 30 kg/m^2 should be counseled on lifestyle changes for weight loss with individualized goals.[50] Abdominal obesity may be considered an indication for weight loss based on the strong association between abdominal girth, metabolic syndrome, and CKD.[51–54] Behavioral changes are central to any weight reduction program, yet maintaining these changes is exceedingly difficult. Common diabetes and CKD comorbidities, such as decreased exercise capacity, often compound the difficulty. Therefore, benefits of even moderate weight loss and a generally healthy lifestyle should be encouraged. Nevertheless, in those with CKD who are overweight, yet not obese, potential benefits of weight loss are currently uncertain. As a practical matter, overweight persons with diabetes and CKD should be counseled about avoiding further weight gain because fatness is associated with inflammation, insulin resistance, hypertension, and dyslipidemia. A variety of balanced healthy diets can be considered for people with diabetes and CKD.[55] Among those who are obese, a reasonable approach for weight loss is to reduce overall intake by about 500 calories per day, which in theory will decrease weight by about 1 pound per week.[56]

Increasing physical activity contributes to weight loss by raising the caloric burn rate.[56] In a case-control study of cardiac rehabilitation, participants with CKD were as likely as those without CKD to lose weight, increase physical activity, and achieve risk factor goals.[57] Another small study of resistance training three times per week in elderly patients with advanced CKD (stage 4 or 5) found that muscular strength increased significantly.[58] Among inactive type II diabetic patients, either aerobic or resistance training was found to improve glycemic control, but the greatest benefit was seen when patients participated in both types of exercise.[59] Potential benefits of exercise to improve weight loss, hyperglycemia, and other risk factors in CKD have recently been reviewed and merit further study.[60]

Special Consideration for Hypoglycemia in the Treatment of Diabetes and Chronic Kidney Disease

The major risk for attaining HbA1c levels greater than 7% is hypoglycemia. Patients with advanced CKD (particularly stages 4 and 5) have increased risks of hypoglycemia for

two major reasons: 1) decreased clearance of insulin and oral agents used to treat hyperglycemia, and 2) impaired kidney gluconeogenesis. With reduced kidney mass, the amount of gluconeogenesis carried out by the kidney is decreased.[17] Reduction in gluconeogenesis reduces the physiological defense to excessive insulin and oral agent dosage or lack of food intake resulting in hypoglycemia. However, this magnitude of this effect is difficult to quantify. About one-third of insulin degradation is carried out by the kidney and impaired kidney function is associated with a prolonged half-life of insulin. Type I diabetic patients receiving insulin who had elevated serum creatinine levels (mean 2.2 mg/dl) were reported to have a fivefold increase in frequency of severe hypoglycemia.[18,19] Therefore, it is imperative that patients monitor their blood glucose levels closely and reduce doses of insulin and oral hypoglycemic agents as needed to avoid hypoglycemia.

Controversies Regarding Management of Hyperglycemia

Assessment and Goals of Glycemic Control in Chronic Kidney Disease

Inaccuracy in the relationship between HbA1c and ambient glucose levels may hinder good glycemic control in diabetic patients with CKD. Various complications of CKD can either raise or lower the HbA1c for a given degree of glycemia. Reduced red blood cell lifespan, hemolysis, and anemia tend to falsely decrease the HbA1c value. Conversely, misleadingly high HbA1c values may be produced by acidosis and carbamylation of hemoglobin.

Several studies have attempted to evaluate the effect of CKD on relationships between HbA1c and glycemia. Morgan and colleagues found that the relationship was not different between patients with normal kidney function and those with nondialyzed kidney failure (mean serum creatinine of 6.6 mg/dl), whereas some hemodialysis patients had lower than expected HbA1c levels relative to their ambient degree of glycemia.[61] However, opposite findings for dialysis patients were reported by Joy and colleagues.[62] Recently, a larger study with greater statistical power confirmed that HbA1c values in hemodialysis patients were indeed lower than in diabetic patients without CKD for the level of glycemia.[63] In contrast, the relationship between blood glucose and glycated albumin was not affected by presence or absence of kidney disease, suggesting that this measure may be a better indicator of chronic glycemia in ESRD.

The HbA1c assay can have inherent biases. In a comparison of different affinity high performance liquid chromatography methods, the Variant II (Bio-Rad Laboratories) method showed a positive bias (0.59% at HbA1c of 6% and 0.88% at HbA1c of 9%), but other methods (Primus CLC330, Diamat, Unimate) have not shown clinically pertinent biases in CKD.[64] Neither peritoneal dialysis nor hemodialysis acutely changes HbA1c levels.[65] As discussed previously, glycated albumin shows promise that merits further investigation and validation as an index of glycemia in CKD and ESRD.[63]

Although patients with advanced CKD or ESRD may no longer prevent loss of kidney function by glycemic control, prevention of other microvascular complications, namely retinopathy and neuropathy, may still be possible. In addition, relatively small studies indicate that survival improves with better glycemic control in patients on peritoneal dialysis or hemodialysis.[66,67] Among hemodialysis patients, HbA1c was a significant predictor of survival hazards ratio ([HR] 1.133 per 1.0% increment of HbA1c, 95% confidence interval [CI] 1.028 to 1.249, $p = 0.012$) after adjustment for age and sex.[67] Yet, recent analyses from large United States national dialysis providers' databases have reached conflicting conclusions regarding level of HbA1c and survival. Williams and colleagues reported that 1-year survival was not influenced by HbA1c in 24,785 patients with type 1 or 1 diabetes.[68] In contrast, Kalantar-Zadeh and colleagues found a strong association between higher HbA1c and increased all-cause mortality risk in 23,618 diabetic hemodialysis patients using a multiple variable model with time-dependent covariates adjusted for case mix and markers of malnutrition, inflammation, and anemia with follow-up extended to 3 years (Figure 11-5).[69] Subsequently, Williams and colleagues published an updated report on 1-year hospitalization risk in their cohort and observed that risk increased at extremes of HbA1c (high or low).[70] A reasonable interpretation of these data is that the HbA1c levels are confounded by comorbidities such as malnutrition, inflammation, and anemia, which make this marker of glycemia less robust in the hemodialysis population. Increased mortality risk at the low end of HbA1c probably reflects severity of illness. However, high HbA1c levels also appear to impart mortality risk in diabetic hemodialysis patients. As such, good glycemic control remains an important objective in this population.

The KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease concluded that assessment of glycemic control in diabetes and CKD, even at advanced stages, should follow the standards of care set by the ADA.[9] In persons receiving multiple insulin injections, self-monitoring of blood glucose (SMBG) is recommended three or more times daily (premeal and bedtime) (see Table 11-1). In those receiving less frequent insulin injections, oral agents, or medical nutrition therapy, SMBG is still useful in achieving glycemic goals. Postprandial SMBG testing may also be helpful, particularly in patients with gastroparesis. The optimal frequency of SMBG has not been established in people with type 2 diabetes who are being treated by oral agents, but the ADA recommends testing sufficiently often to reach glycemic goals.[9] In addition, HbA1c levels should be determined at least twice per year in stable patients who are at goal, and more often (approximately every 3 months), in patients whose therapy has changed or who are not at goal. Due to the complexity of interpreting HbA1c levels in patients treated by hemodialysis (and likely peritoneal dialysis), SMBG assumes particular importance for assessment of glycemic control in the ESRD setting.

Glycemic Control in the Setting of Type II Diabetes and High Chronic Kidney Disease Risk

A major controversial issue is the effect of intensive glycemic control on CVD risk in patients with type 2 diabetes. Three landmark clinical trials in patients with type 2 diabetes and CVD or multiple risk factors were recently been

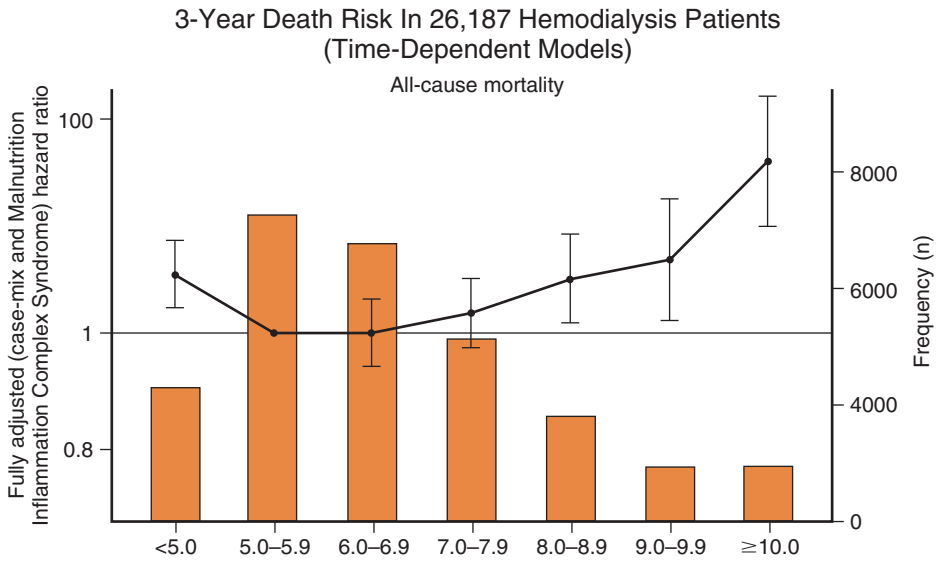


FIGURE 11-5 Three-year death risk by hemoglobin A1c level in hemodialysis patients (n = 26,187) based on time-dependent models adjusted for case-mix and markers of inflammation and malnutrition. (Adapted from K. Kalantar-Zadeh, J. Kopple, D. Regidor, et al., A1C and survival in maintenance hemodialysis patients, Diabetes Care 30 [2007] 1049–1055.)

reported: Action to Control Cardiovascular Risk in Diabetes (ACCORD, n = 10,521, Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (ADVANCE, n = 11,140, and Veterans Affairs Diabetes Trial (VA-DT, n = 1791.[71–73] The principal hypothesis driving these trials was that intensive glycemic control to near-normal levels should reduce risk of major CVD events and death. The results of all three studies were negative. Not only did intensive glycemic control fail to improve CVD outcomes, but also ACCORD was suspended 17 months early due to increased risk of death from any cause and CVD (Figure 11-6). Although risk of nonfatal MI was reduced, there were greater numbers of fatalities from MI, congestive heart failure, and cardiac procedures in ACCORD participants treated intensively, suggesting that the MI case-fatality rate could have actually increased.[71] A major safety concern in this triad of trials was a high rate of severe hypoglycemic episodes in patients treated with intensive glycemic control.[71–73] In ACCORD, for example, the frequency of events defined by neurological compromise requiring assistance was 16% in the intensive therapy group versus 5% in the standard therapy group ($p < 0.001$).

To put the ACCORD, ADVANCE, and VA-DT studies in context, key aspects of their populations and interventions should be appreciated. These studies enrolled older type 2 diabetic patients (mean age >60 years), about one-third (or more) of whom had a previous CVD event.[71–73] In ADVANCE, DKD as defined by macroalbuminuria was present in 3.4% (intensive control) and 3.9% (standard control), whereas microalbuminuria was present in 27% of each group.[72] Baseline albuminuria levels were not reported in the main ACCCORD and VA-DT papers.[71,73] Patients were excluded from ACCORD for a serum creatinine level greater than 1.5 mg/dl and from VA-DT for a serum

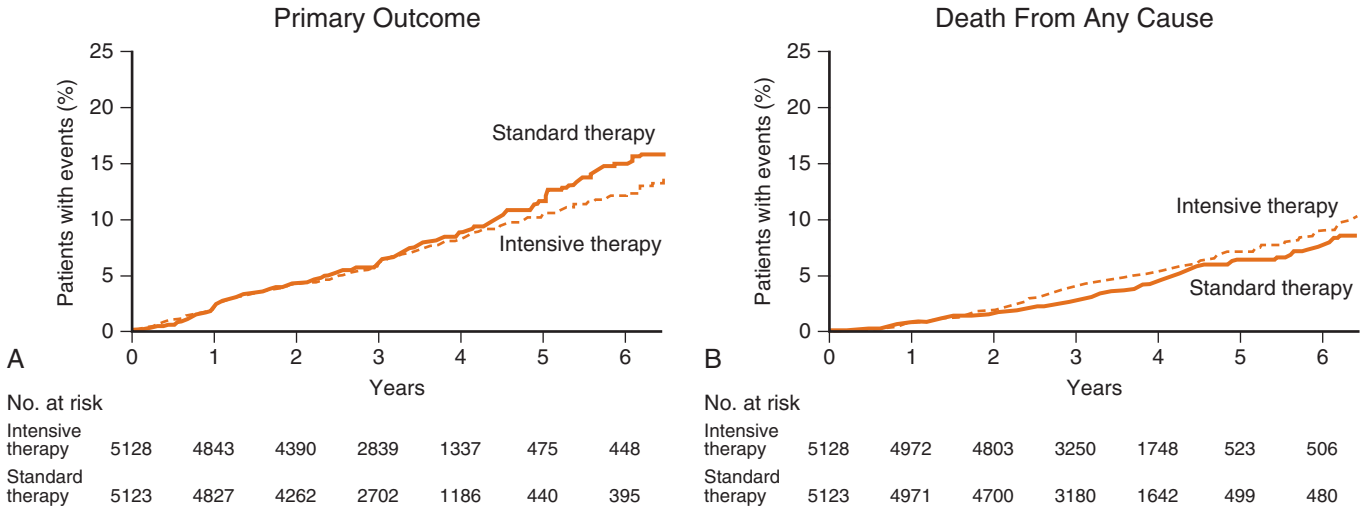


FIGURE 11-6 Kaplan-Meier survival curves by study group assignment in the ACCORD trial. **A,** The primary outcome (nonfatal myocardial infarction, nonfatal stroke, CVD death), intensive glycemic control to standard therapy (hazard ratio 0.9; 95% confidence interval 0.78 to 1.04, p = 0.16); **B,** Death from any cause, intensive glycemic control to standard therapy (hazard ratio 1.22; 95% confidence interval 1.01 to 1.76, p = 0.02). (Adapted from The Action to Control Cardiovascular Risk in Diabetes [ACCORD] Study Group, Effects of intensive glucose lowering in type 2 diabetes, N. Engl. J. Med. 358 [2008] 2545–2559.)

creatinine level greater than 1.6 mg/dl. At baseline, kidney function (as measured by serum creatinine) appeared "normal" on average in the three studies. The trials aimed to reduce HbA1c to between 6% and 6.5% in the intensive treatment groups compared to standard treatment that reflected prevailing practice. Achieved median HbA1c values were 6.3-6.9% and 7.0-8.5%, respectively. Multiple drugs were used in both arms of each study.

The main difference between studies was that death and fatal CVD outcomes were even more likely (i.e., increased risk of harm) in the intensively-treated group in ACCORD, whereas intensive therapy was essentially risk-neutral in ADVANCE and VA-DT.[71–73] Greater risk of adverse CVD outcomes may have been related to the intensive glycemic control *strategy* in ACCORD. Possible reasons for exacerbated CVD risk include level of glycemia achieved, magnitude or rate of change in glycemia, drug usage or interactions, severity and frequency of hypoglycemia, weight gain, and fluid retention. Increased risk of death was not attributable to any specific drug, rosiglitazone in particular.[71]

Despite the unexpected primary trial results and safety concerns, select type II diabetic patients may benefit from intensifying glycemic control to near-normal levels.[74] Patients without known CVD or shorter diabetes duration, or with less severe hyperglycemia, may be reasonable candidates for more intensive control with a goal of reducing microvascular disease risk. Of note, risk of new onset microalbuminuria and new or worsening nephropathy (primarily progression to macroalbuminuria) decreased in ADVANCE.[72] However, albuminuria-related outcomes are not clinical endpoints in the sense of defining morbidity or mortality.[75] In the absence of apparent benefits on kidney function or failure, the value of "normalizing" glycemia remains arguable in type II diabetic patients at high CVD risk. Additionally, the benefit-to-risk ratio of intensive glycemic control is more uncertain in patients with diabetes and CKD because the trials excluded those with measurably decreased kidney function.

Early reports from the DCCT/EDIC study and the UKPDS did not initially inspire confidence that the risk of CVD was reduced by intensive glycemic control.[10,12,13] However, recent accounts of posttrial, long-term follow-up indicate that risks of death and CVD events were in fact diminished by intensive glycemic control long after the interventions concluded (at least 10 year follow-up), a so-called legacy effect.[8,14] These risk reductions were achieved even though differences in HbA1c between study groups disappeared by 1 year after the end of the interventions.

How can results from DCCT/EDIC and UKPDS be reconciled with those from ACCORD, ADVANCE, and VA-DT?[8,14,71–73] Three principal reasons are likely to account for the differences between study outcomes: 1) **Lower risk characteristics of study populations in DCCT/EDIC (young type 1 diabetic patients) and UKPDS (patients with new onset type 2 diabetes)**. Both studies had exclusion criteria for CVD. DCCT/EDIC also excluded patients with hypertension or hypercholesterolemia. Similarly, lower risk subgroups in ACCORD appeared to have reduced risk of MI, stroke, or CVD death with intensive glycemic control. 2) *Less intensive glycemic control in DCCT/EDIC and UKPDS.* For example, the mean HbA1c at the end of the intensive intervention in UKPDS was 8.2% and remained between 7.5% and 8.5% over long-term follow-up in both conventional and intensively treated groups. Thus, "intensive" therapy in UKPDS was akin to "standard" therapy in ACCORD and ADVANCE. There seems to be a point below which further benefits do not accrue and risks increase with intensive glycemic management. 3) *Longer duration of follow-up in DCCT/EDIC and UKPDS.* Intensive glycemic control did not improve CVD outcomes or decrease risk of death until more than 10 years of follow-up. The median durations of follow-up in ADVANCE, ACCORD, and VA-DT may have been too short to assess long-lasting effects. Indeed, ADVANCE data suggest that CVD and death could be less frequent after 5 years of intensive glycemic control, but this observation must be considered hypothesis-generating.[72]

Since publication of ACCORD, ADVANCE, and VA-DT, the ADA has stood by its recommendation for a goal HbA1c less than 7%, but it also emphasizes the importance of liberalizing this target in groups at greater risk of hypoglycemia.[74] Because diabetic patients with CKD are at particularly high risk of hypoglycemia, and of CVD and death, these recent trials raise a red flag about attempts to "normalize" glycemia in such a high-risk population. Even if long-term benefits should emerge, there may be a grave up-front price of overly intensive glycemic control. Future studies should address fundamental questions about strategies for glycemic control (level, magnitude and rate of change, specific drugs, duration). Participants with CKD should noticeably be included in these studies considering that some 30% to 50% of people with diabetes have, or will develop, kidney disease.

Management of Other Diabetic Complications in the Setting of Chronic Kidney Disease

The full spectrum of micro- and macrovascular complications is common in diabetic patients with CKD. A comprehensive approach to diabetic care requires the same regular surveillance and treatment of these complications in those with CKD as it does for other patients.

Microvascular Disease

Screening and treatment of retinopathy and foot care are essential to optimal care. Absent specific data in the CKD subpopulation, the KDOQI guidelines and recommendations recommended following the general standards set by the ADA (Table 11-4).[1,9] An ophthalmologist or optometrist who is knowledgeable and experienced in the diagnosis and management of diabetic retinopathy should perform a comprehensive dilated eye exam annually. Patients should be educated about the importance of foot surveillance and ulcer prevention with an emphasis on self-management. The feet should be examined visually at each healthcare visit. A comprehensive foot and vascular exam including visual inspection, Semmes-Weinstein monofilament testing, use of a 128 mHz tuning fork for testing of vibratory sensation, and evaluation of pedal pulses should be performed annually. Because the risk of ulcers and amputations is high in those with diabetes and CKD, referral to foot care specialists for annual examinations and preventive care is prudent.

TABLE 11-4 ADA Recommendations for Assessment of Retinopathy and Foot Care

COMPLICATION	EVALUATION	SETTING	FREQUENCY
Retinopathy	Comprehensive dilated eye exam	Ophthalmologist or optometrist who is knowledgeable and experienced in diabetic retinopathy	Annually
Foot ulcers*	Visual inspection	Self-management	Daily
	Visual inspection	Healthcare encounters	Each visit
	Semmes-Weinstein monofilament testing, 128 mHz tuning fork	Healthcare encounters	Annually
	Pedal pulses†	Healthcare encounters	Annually
	Comprehensive exam and preventive care	Refer high-risk patients to foot and/or vascular specialists*	Annually, more often as needed

*High-risk patients include those with CKD, CVD, peripheral vascular disease, neuropathy with loss of protective sensation, reduced ankle-brachial index, altered biomechanics, callus, bony deformity, nail pathology, retinopathy, diabetes duration greater than 10 years, and poor glycemic control.
†Consider obtaining an ankle-brachial index at initial screening for peripheral arterial disease, as many patients with peripheral arterial disease are asymptomatic.
(Adapted from National Kidney Foundation—Kidney Disease Outcomes Quality Initiative [NKF-KDOQI], Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease, Am. J. Kidney Dis. 49 [2007] S1-S179.)

Macrovascular Disease

Macrovascular disease, or CVD, is the predominant cause of death in patients with diabetes and CKD. Evaluation and management of CVD in CKD is comprehensively addressed in Chapter 10. The intent of this section will be to highlight topics of particular importance in the setting of diabetes.

Diagnostic Testing for Coronary Heart Disease in Diabetic Patients

The ADA recommends screening for coronary heart disease in diabetic patients with typical or atypical ischemic symptoms or an abnormal resting ECG.[9] Whether asymptomatic patients with diabetes should undergo diagnostic testing for coronary heart disease has been controversial. Diabetic patients with silent ischemia, especially if accompanied by cardiac autonomic neuropathy, have a poor prognosis. However, data indicating that screening asymptomatic patients improves prognosis beyond risk factor evaluation and management is lacking. The American Heart Association (AHA) has not endorsed diagnostic testing for coronary heart disease in asymptomatic diabetic patients because of this lack of evidence.[76] The presence of traditional CVD risk factors did not predict silent ischemia in the cross-sectional Detection of Ischemia in Asymptomatic Diabetics (DIAD) study.[77] Furthermore, an interim report of repeat nuclear imaging found that 79% of initially abnormal perfusion scans (inducible ischemia) reverted to normal after 3 years in DIAD.[78] Most recently, the longitudinal results of DIAD revealed that screening of asymptomatic diabetic patients did not reduce CVD death or nonfatal MI over a mean follow-up of nearly 5 years.[79]

A noninvasive approach to diagnostic testing is preferred as the first step in evaluating coronary heart disease in diabetes. According to the AHA and the ADA, stress testing with exercise ECG should be the initial strategy.[9,76] Those who have nondiagnostic exercise ECG tests may benefit from the addition of an imaging modality (nuclear perfusion scan or echocardiography) to the exercise protocol.[76] Many diabetic patients with advanced CKD or ESRD have poor exercise tolerance and left ventricular hypertrophy. For such patients who cannot exercise adequately, pharmacological stress testing (dobutamine or dipyridamole) with imaging is indicated.[76,80] Coronary angiography may be performed if evidence for clinically significant IHD is detected or for diagnostic uncertainty. Persons with diabetes and CKD are at high risk for acute kidney injury due to RCN. Whenever possible, preventive strategies should be employed to mitigate this risk (see Chapter 48). Nevertheless, considering the extremely high CVD risk in diabetes and CKD, angiography should not be avoided if clinical indications for the invasive assessment or treatment of IHD are present.

Management of Coronary Heart Disease in Diabetic Patients

Medical management of coronary heart disease in diabetes largely follows the same approach as for nondiabetic patients. Delving further into the subset with both diabetes and CKD, the limited amount of available evidence supports similar strategies that include ACE inhibition or ARB therapy after MI complicated by left ventricular dysfunction and for chronic coronary heart disease, beta blockers after MI, and aspirin for primary and secondary prevention.[76,81–87] As a precautionary note, the risks of hypoglycemia brought to the fore by clinical trials (ACCORD, ADVANCE, VADT) should prompt careful assessment for hypoglycemic unawareness that could predispose to severe episodes in beta-blocker treated patients.[71–73]

Acute outcomes of revascularization for MI or acute coronary syndromes do not appear to vary by diabetes status in CKD. However, evidence to guide treatment of patients with CKD is sparse. Despite their high risk of death and complications, those with CKD are less likely to receive reperfusion or other recommended therapies.[88–91] However, when these therapies have been given to persons with CKD, the risk of death was decreased in observational studies.[88,89,91] Data specifically for the subset of patients with both diabetes and CKD do not exist. This population should be included in future clinical trials of treatment for acute cardiac ischemia to define benefits and risks. In the meantime, the current standard-of-care (reperfusion and antiplatelet strategies) should be considered for diabetic patients with CKD unless specific contraindications exist.

Optimal methods of coronary artery revascularization in the nonacute setting are controversial. Data specifically concerning persons with diabetes and CKD are lacking, but for those with

either diabetes or CKD, coronary artery bypass surgery has been considered superior to percutaneous transluminal angioplasty for multiple-vessel disease.[76,92,93] The KDOQI Guidelines for Cardiovascular Disease in Dialysis Patients came to a similar conclusion, while recommending research to include prospective, controlled trials of newer stenting technologies.[80] Much of the benefit of coronary artery bypass surgery in diabetes or advanced CKD appears to be derived from use of the internal mammary artery. However, in a recent subgroup analysis of a prospective clinical trial, the Arterial Revascularization Therapies Study (ARTS), patients with calculated creatinine clearance less than 60 ml/min/1.73m^2 had similar survival free of death, myocardial infarction, or stroke whether they were randomized to either coronary artery bypass surgery or percutaneous coronary intervention with multiple-vessel stenting.[94] Only repeat revascularization was less frequent with coronary artery bypass surgery.

Although controlled trials of revascularization procedures are nonexistent for persons with both diabetes and CKD, the excess cardiovascular risk and deaths associated with diabetes after percutaneous coronary interventions were predominantly driven by the subset with proteinuria in a large, observational cohort study.[95] This group of patients should be included in clinical trials of innovative revascularization technologies in the future. In the meantime, either coronary artery bypass grafting or stenting (single- or multiple-vessel) may be acceptable methods of revascularization in persons with diabetes and CKD.

Intensive Glycemic Control in the Acute Care Setting

Glucose-insulin-potassium (GIK) infusion and intensive glycemic control have been advocated for reducing mortality risk after acute MI or with critical illness (especially after cardiac surgery) in persons with and without diabetes.[96,97] Although professional societies concerned with management of diabetes in the acute care setting responded quickly to recommend near-normalization of blood glucose within 24 to 48 hours after MI, more recent evidence has not substantiated this approach. Benefits of GIK therapy were described in relatively small studies or metaanalyses in which the reduction in mortality risk had wide confidence intervals, indicating uncertainty in the conclusions.[98]

The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) and the Estudios Cardiologicas Latin America Study Group (ECLA) formally merged into a single trial, CREATE-ECLA, that randomized over 20,000 patients with acute MI to receive or not to receive GIK therapy.[99] In this large trial, no benefits on death or reinfarction were observed after 30 days in the group as a whole or in predefined subgroups, including diabetes. Similarly, survival benefits of intensive insulin therapy in critical illness were not verified in patients admitted to a medical intensive care unit (ICU), irrespective of diabetes status, CVD, or kidney disease diagnosis.[100] In a larger follow-up study of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, DIGAMI 2, the survival benefit of intensive glycemic control after MI in diabetic patients was not confirmed.[101] A metaanalysis of 29 randomized controlled clinical trials of tight glycemic control in critically ill adults found no benefit on survival or need for dialysis irrespective of whether patients were treated in medical or surgical intensive care units or the intensity of tight glycemic control.[102] Tight glycemic control was found to reduce relative risk of sepsis by approximately 26% (10.9% versus 13.4%), whereas risk of severe hypoglycemia (blood glucose <40 mg/dl) was increased approximately fivefold (13.7% versus 2.5%). Finally, the Nomoglycemia in Intensive Care—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was an international trial that enrolled over 6000 adults admitted to intensive care units (about 20% with diabetes).[103] Participants were randomized to a target blood glucose level of 81 to 108 mg/dl (intensive control) or less than 180 mg/dl (conventional control) accomplished by intravenous insulin infusion. Intensive glycemic control (mean achieved blood glucose of 107 mg/dl) increased relative risk of death at 90 days by about 15%, and absolute risk by 2.6%, compared to conventional control (mean achieved blood glucose of 142 mg/dl). The number needed to harm (death) was 38. Relative risk of severe hypoglycemia was increased almost 15-fold (6.8% versus 0.5%). No reduction in risk of sepsis, need for dialysis or mechanical ventilation, length of stay in the intensive care unit, or other prespecified clinical endpoints were favorably influenced intensive glycemic control. Outcomes did not vary by prespecified subgroups, including those with diabetes.

Patients with CKD are at particularly high risk of hypoglycemia and related comorbidities with intensive glycemic control regimens. The ADA Standards of Care were updated in 2010 to reflect uncertainties raised by the recent clinical trials. The most recent guidance is to aim for a blood glucose range of 140-180 mg/dl in critically ill patients.[9] Considering the increased risk of hypoglycemia and lack of verifiable clinical benefit, more intensive glycemic control regimens in acute care settings (including MI) should be avoided in diabetic patients with CKD.

Hypertension in Diabetes Chronic Kidney Disease

Hypertension is a chief risk factor for CKD, which along with hyperglycemia, must be optimally managed to reduce risk of serious diabetic complications. Although management of hypertension is extensively addressed elsewhere in this textbook, several recent publications particularly relevant to care of diabetic patients with, or at-risk for, CKD will be discussed here.

The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) Trial

This phase II study evaluated the effect of intensifying inhibition of the renin-angiotensin system by adding renin inhibition to the current standard-of-care including background treatment with the ARB losartan.[104] Patients with type 2 diabetes, macroalbuminuria, and hypertension were randomized to either receive the oral renin inhibitor, aliskiren, or placebo for 6 months. The aliskiren group achieved the primary endpoint of albuminuria lowering by 25%, whereas there was no change in albuminuria in the placebo group. This trial is important because it explored a new treatment that potentially could improve the outlook for patients with diabetes and CKD. However, before embracing aliskiren as

a specific treatment for DKD, certain limitations must be recognized. First, the primary outcome of the study was albuminuria, which is a widely accepted biomarker of DKD, not a clinical endpoint. Findings of this phase II study encourage investigation of aliskiren for DKD in phase III trials that are driven by clinical endpoints (death, ESRD, loss of kidney function, cardiovascular events). Second, albuminuria is an imperfect biomarker because its relationship to clinical outcomes is not necessarily consistent across different settings such as various stages of DKD or types of treatments. More reliable biomarkers would be welcome, as it is difficult to obtain sufficient data within a reasonable timeframe in clinical endpoint studies of chronic diseases such as DKD. Third, older mean age and longer mean duration of diabetes mellitus in placebo-treated participants could have increased resistance to albuminuria reduction and consequently, might have introduced bias in favor of aliskiren. Fourth, subgroup analysis suggests that nonwhite participants might not have benefited from aliskiren treatment as much as white patients, but this finding may reflect the fact that this analysis was underpowered. Finally, clinically relevant hyperkalemia (>6 mmol/l) was slightly more common in the aliskiren group than in the placebo group. In summary, aliskiren reduced the urinary albumin-to-creatinine ratio in patients with DKD when given in combination with an ARB. Efficacy and safety are yet to be established in phase III trials driven by clinical endpoints. Aliskiren could be a salutary addition to therapy if risks of untoward consequences of DKD prove to be safely reduced in large, long-term studies.

The Avoiding Cardiovascular Events through Combination (ACCOMPLISH) Trial

High-risk hypertensive patients, defined by a clinical diagnosis of CVD or diabetes, were randomized to receive an ACE inhibitor (benazapril) in combination with either a calcium channel blocker (amlodipine) or a diuretic (hydrochlorothiazide).[105] This large, multinational clinical trial enrolled 11,506 participants of whom 60% had diabetes. Excellent blood pressure control was achieved in both groups (mean blood pressure was 132/74 mmHg). The benazepril/amlodipine combination was superior for reducing death and CVD endpoints compared to the benazepril/hydrochlorothiazide combination (primary outcome 9.6% versus 11.8%, relative risk reduction of approximately 20%). However, the trial allowed loop diuretic administration, and most diabetic patients require diuretic therapy to achieve the recommended blood pressure goal of less than 130/80 mmHg. Considering the overlap of this clinical trial group with the diabetes and CKD population, adding a calcium channel blocker such as amlodipine to treatment with ACE inhibition is a reasonable consideration for controlling blood pressure and reducing CVD risk.[106] A pre-specified secondary analysis of renal outcomes also found that the benazapril/amlodipine combination group had reduced risk of doubling of serum creatinine, eGFR <15 ml/min/1.73 m^2, or need for dialysis compared to benazapril/hydrochlorothiazide (2.0% versus 3.7%, relative risk reduction of almost 50%). However, albuminuria decreased more in the ACE inhibitor and diuretic combination group. Macroalbuminuria in patients with type 2 diabetes is the condition in which albuminuria changes have been most evidently related to clinical endpoints. Although more than half of participants in the ACCOMPLISH trial had diabetes, macroalbuminuria was rare (5%). Data such as these raise doubt about use of albuminuria as a surrogate outcome for clinical CKD events across different stages and settings of CKD.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)

Ramipril was the active comparator versus telmisartan or the combination of both drugs (dual renin-angiotensin system blockade) in high-risk patients defined by CVD or diabetes and "end-organ damage." This was a large randomized, controlled clinical trial (n=25,620) that included 38% with diabetes of whom 12% had macroalbuminuria.[107,108] Telmisartan was noninferior to ramipril for a number of endpoints related to CVD (cardiac death, MI, stroke, congestive heart failure) and CKD (all-cause death, ESRD, doubling of serum creatinine). Risk of new onset albuminuria (micro- or macro-) was reduced by combination therapy compared to ramipril.[108] Both telmisartan and combination therapy reduced frequency of progression of albuminuria more than ramipril.[108] Even so, in the overall study and among subgroups, combination therapy was actually associated with either kidney-related harms or no benefit compared to ramipril.[108] Loss of eGFR was greater with either telmisartan or combination therapy than with ramipril alone. Other harms of combination therapy included increased risk of adverse kidney events (death, ESRD, doubling of serum creatinine) in the overall group and low-renal-risk subgroups (no diabetes, hypertension, or CKD). High-renal-risk subgroups, including "overt diabetic nephropathy" or CKD stage 3 or greater, did not benefit from combination therapy. Notably, reductions in albuminuria by combination therapy or telmisartan were discordant from clinical endpoints in that either no, or no greater, benefits were observed. Additionally, risks of important side effects such as hypotension (telmisartan and combination therapy) and hyperkalemia (combination therapy) were increased compared to ramipril alone. This study raises valid questions about long-term, dual renin-angiotensin system blockade with ACE inhibition and ARB: Is the combination safe? Is albuminuria is a reliable disease marker in this setting?

Primary Prevention of Diabetic Kidney Disease: Blood Pressure versus Renin Angiotensin System Inhibition

Diabetic patients without elevated levels of urinary albumin or with low-level microalbuminuria may not have underlying DKD. As such, these populations can be considered for "primary prevention" of overt DKD. An analysis of studies evaluated effects of ACE inhibition versus placebo, ACE inhibition versus an active comparator for blood pressure control, and ACE inhibition with addition of "intensive blood pressure control."[109] Data linking albuminuria changes to clinical endpoints (death, ESRD, doubling of serum creatinine) were nonexistent in primary prevention studies. Evaluation of kidney disease markers (albuminuria and measures of GFR) found that ACE inhibition provided greater benefits when blood pressure was lowered more. However, differences

in albuminuria or GFR measures were not observed when blood pressure did not vary between ACE inhibition and comparator groups (placebo or active treatment). Therefore, the available body of evidence indicates that early treatment of hypertension, rather than use of specific agents such as ACE inhibitors, appears to be of prime importance in preventing onset of kidney disease in the diabetic population. Even more recently, the Renin-Angiotensin System Study (RASS) and the Diabetic Retinopathy Candesartan Trials (DIRECT) found no benefit of ACE inhibition or angiotensin receptor blockade on preventing new-onset microalbuminuria in either type 1 or 2 diabetic patients with normal blood pressure or well-controlled hypertension. RASS included renal biopsies, which correspondingly showed no benefit of renin angiotensin system inhibitors on structural parameters representative of diabetic glomerulopathy.[110,111]

Importance of Dietary Sodium

The KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease recommend a version of the Dietary Approaches to Stop Hypertension (DASH) diet with modifications for DKD.[1,112] Dietary sodium reduction to 2.3 g/d (100 mmol/d) is recommended because most patients with diabetes have hypertension characterized by enhanced sodium retention. The CKD modifications of the DASH diet decreased target dietary protein from 1.4 g/kg body weight per day to 0.8 g/kg body weight per day, and restricted phosphorous (0.8 to 1 g/d) and potassium (2 to 4 g/d).[1] Phosphorous binders may be needed in patients with advanced CKD because of emphasis on whole grains and dairy products.

Dyslipidemia in Diabetes and Chronic Kidney Disease

Diabetes greatly increases the risk for premature disability and death.[6] Most diabetic patients die of CVD, and although mortality rates have declined over the last five decades, diabetes still imparts a twofold to fourfold excess risk of CVD death.[113,114] CKD only increases this risk further.[4] Therefore, in addition to diabetes, CKD can be considered a "CVD risk amplifier."[1,4,80] Therefore, strategies to prevent CVD, particularly treatment of dyslipidemia, are essential to optimal care of diabetic patients with CKD. Guidelines for use of lipid-lowering agents in CKD stages 1 to 4 due to diabetes or other causes are generally similar, although currently there is no direct or indirect evidence for treating patients in CKD stage 4.[1,9,115,116] Notably, the rationale for lipid-lowering drug therapy in this setting is limited to CVD prevention because evidence is insufficient for CKD risk reduction. Therapeutic lifestyle change is an important component of the therapeutic approach to dyslipidemia in patients with diabetes and CKD, as it is for others.

Statin Therapy for Diabetic Patients with Chronic Kidney Disease stages 1 to 4

Primary and secondary CVD prevention trials, including those in persons with diabetes, have documented substantial cardiovascular benefit from administration of statins.[117–120] The primary prevention Collaborative Atorvastatin Diabetes Study (CARDS) reported an impressive decrease in CVD deaths in persons with type 2 diabetes in the absence of markedly decreased kidney function.[121] In terms of absolute risk reduction, patients in the Heart Protection Study (HPS) with diabetes and CVD received the greatest benefit from statin therapy.[117]

Posthoc analyses from the Pravastatin Pooling Project, a subject-level database combining results from three randomized trials of pravastatin 40 mg daily versus placebo included 19,737 subjects of whom 4099 (20.8%) had CKD but not diabetes at baseline, 873 (4.4%) had diabetes but not CKD, and 571 (2.9%) had both conditions.[125] CKD was defined by eGFR less than 60 ml/min/1.73 m^2, or eGFR 60 to 89.9 ml/min/1.73 m^2 with trace or greater proteinuria by dipstick. The primary composite outcome was time to MI, CVD death, or percutaneous or surgical coronary revascularization. The incidence of the primary outcome was lowest in individuals with neither CKD nor diabetes (15.2%), intermediate in subjects with only CKD (18.6%) or only diabetes (21.3%), and highest in subjects with both characteristics (27.0%). Pravastatin significantly reduced the risk of the primary outcome by 25% in subjects with CKD and concomitant diabetes and by 24% in subjects with neither characteristic. The absolute reduction in risk of the primary outcome due to pravastatin use was highest in subjects with both CKD and diabetes (6.4%). Therefore, the Pravastatin Pooling Project provides indirect evidence that pravastatin treatment effectively decreases risk of CVD in diabetes with CKD stages 1 to 3. However, it does not provide evidence for a protective effect of pravastatin with more advanced CKD because these patients were excluded from the trials. Patients with advanced stages of CKD were also excluded from the West of Scotland Coronary Prevention Study (WOSCOP), a primary prevention trial, and from the Cholesterol and Recurrent Events (CARE) study and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, both secondary intervention studies.[122–124]

On this basis, the KDOQI guidelines recommended that patients with diabetes and CKD (stages 1 to 4) receive low-density lipoprotein (LDL) cholesterol-lowering therapy.[1] The high CVD risk associated with diabetes and CKD supports initiation of statin therapy when LDL cholesterol is greater than 100 mg/dl, with a therapeutic option to achieve an LDL cholesterol goal of less than 70 mg/dl.

Statin Therapy in Diabetic Patients on Hemodialysis

The 4D study, a multicenter randomized, double-blind, placebo-controlled trial, randomly assigned 1255 patients with type 2 diabetes on maintenance hemodialysis to receive 20 mg atorvastatin per day or placebo.[125] After 4 weeks of treatment, atorvastatin reduced the median LDL-C level by 42% whereas the placebo group had a 1.3% reduction. At least 1 mmol difference in LDL-C was maintained throughout the treatment period. During a median follow-up of 4 years, 469 patients (37%) reached the primary endpoint (a composite of CVD death, nonfatal MI, fatal and nonfatal stroke), 226 of whom were assigned to atorvastatin and 243 of whom were assigned to placebo (relative risk [RR] 0.92, 95% CI 0.77 to 1.1, $p = 0.37$). Atorvastatin had

no effect on the single components of the primary endpoint with the exception of fatal stroke, for which the relative risk increased to 2.03 (95% CI 1.05 to 3.93, p = 0.037). Secondary endpoints including combined CVD events (RR 0.82, 95% CI 0.68 to 0.99; p = 0.03) were reduced, but not combined cerebrovascular events (relative risk [RR] 1.12, 95% CI 0.81 to 1.55; p = 0.49) or total mortality (RR 0.93, 95% CI 0.79 to 1.08, p = 0.33). Despite a high rate of CVD endpoints and the pronounced LDL-C lowering by atorvastatin, a significant reduction of the incidence of the composite primary outcome was not achieved. The unexpected finding of an increase in fatal stroke requires further study. The 4D study was the first large-scale CVD endpoint trial that did not show overall benefit from administration of statin therapy.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) trial included 2776 participants of whom approximately 25% had diabetes. AURORA similarly found no reduction in risk of major CVD events or death over median follow-up of 3.8 years with rosuvastatin therapy at 10 mg per day in either the entire study group or any prespecified subgroup, including diabetes.[126] Contrary to 4D, the AURORA trial found no overall increase in fatal or non-fatal stroke. However, among the diabetic patients, there was a small increase in hemorrhagic strokes among those who received rosuvastatin (12 versus 2 events, p = 0.07). The stroke risk in diabetic hemodialysis patients treated with statins is an important issue worthy of more study and safety monitoring.

The 4D and AURORA trials did not confirm the broadly accepted assumption that for every 30 mg/dl change in LDL cholesterol, the relative risk for CVD is reduced proportionally. Rather, these results are in accordance with observational data in patients on hemodialysis that do not necessarily link dyslipidemia with reduced survival; indeed opposite trends have been noted.[126] Yet, the 4D and AURORA results are contrary to an observational analysis of hemodialysis patients in the United States Renal Data System Morbidity and Mortality Study, Wave 2, which found that the risk of CVD death decreased by 36% in statin users.[127] These findings illustrate the difficulty of basing treatment decisions on observational studies.[127,128,129] The pathogenesis of CVD in patients with diabetes on hemodialysis may differ from that in patients with earlier stages of CKD. This important consideration is worthy of further investigation.

Due to the 4D study results, the KDOQI did not recommend initiation of statin therapy in diabetic patients treated by hemodialysis. However, this recommendation does not preclude statin usage in dialysis patients with specific CVD indications (post-MI), extremely high LDL cholesterol (>190 mg/dl), or those already on treatment.

Newer Cholesterol-Lowering Agents

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial evaluated the combination of ezetimibe, a newer agent that lowers cholesterol by decreasing intestinal absorption, and simvastatin therapy for LDL cholesterol reduction in patients with heterozygous familial cholesterolemia.[130] The unanticipated finding from this study was that the combination treatment was no better at preventing progression of carotid intimamedial thickness, despite more effective LDL cholesterol lowering. It is important to recognize that this was a study of a disease marker, not clinical events. Endpoint-driven studies such as SHARP, a clinical trial of patients with CKD (diabetic and nondiabetic), are presently evaluating the combination of ezetimibe and simvastatin. This is a vital issue for study because ezetimibe could conceivably be useful to lower LDL cholesterol, especially when higher dose statin therapy may be precluded by advanced CKD, kidney transplant, and drug interactions.

Dietary Fat Intake

The AHA recommends that patients at high risk for CVD limit saturated fat to less than 7% of calories and cholesterol to less than 200 mg/day.[131] This advice is appropriate for patients with diabetes and CKD, considering their high-risk status. In addition to concerns about effects of excess dietary protein on the kidney (discussed hereafter), animal meat consumption should be limited to lessen intake of saturated fat and cholesterol and because of its association with all-cause and CVD mortality.[132] Nonfat or low-fat dairy products are also preferred over their full-fat counterparts.

The optimal distribution of calories between fatty acid classes remains to be determined. Dietary recommendations usually combine polyunsaturated fatty acids together without differentiating between categories. A few small, short-term studies have examined effects of fatty acid intake or supplements on markers of kidney disease or risk factors.[133–137] Available evidence suggests that increased intake of omega-3 and monounsaturated fatty acids may have favorable effects on kidney disease progression. Fatty acid intake can be modified by substituting canola oil, a blend that includes both omega-3 and monounsaturated fats, for other vegetable oils. For example, salad dressings and butter replacement products made from canola oil are widely available. The Institute of Medicine has established guidelines for intake of omega-3 fatty acids that recognize significant variances in physiological potency. Adequate intake of alpha-linolenic acid was established as 1.6 g/d for men and 1.1 g/d for women, with substitution of up to 10% of these amounts by the more physiologically potent eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[34] The AHA and KDOQI recommend including one serving of cold-water fish in the diet three times per week to augment intake of EPA and DHA.[80,138] This much cold-water fish (e.g., salmon, mackerel, herring, tuna) would provide EPA and DHA in excess of the 10% of adequate intake amounts. Harms from this range of EPA or DHA are not known, but accumulation of high levels of mercury or other fish contaminants is a latent concern.

Specific Nutritional Issues in Diabetes and Chronic Kidney Disease: The Dietary Protein Debate

In addition to effects of nutrition on CKD and CVD risk factors previously discussed, diet has other notable effects on the kidney in diabetes. Perhaps the most important is that

of dietary protein, which may exacerbate or induce kidney damage when consumed in excess, and conversely, may have a therapeutic benefit if intake is controlled to a healthful amount.

Studies of "low protein" diets for CKD have been reported for more than 20 years. However, many of these studies were limited by small sample size, short duration, and marginal adherence. Nevertheless, the overall impact of these diets has been assessed in a series of evolving metaanalyses. In an early report by Pedrini and colleagues, dietary protein restriction was demonstrated to prevent progression (loss of GFR or increased albuminuria and proteinuria) with a more pronounced benefit in diabetic than nondiabetic kidney disease.[139] A subsequent metaanalysis by Kasiske and colleagues, which focused on indicators of GFR, showed that dietary protein restriction was most effective among persons with DKD.[140] Most recently, Pan and colleagues performed a metaanalysis limited to studies of DKD that were of at least 6 months duration, included a randomized control group, and reported measures of kidney function along with albuminuria and proteinuria.[141] HbA1c and albuminuria/proteinuria, both recognized predictors of clinical outcomes in diabetes, were improved by reducing protein intake. Although no effect on GFR was demonstrated, the discriminatory capacity of this analysis was limited by inclusion of patients with a wide range of kidney function from those with hyperfiltration to stage 3 CKD. Fouque and colleagues have performed a succession of metaanalyses of low-protein diet primarily in nondiabetic CKD.[142–144] Because creatinine-based measures of kidney function were commonly used, yet can be confounded by effects of protein intake on creatinine generation and excretion, the primary outcome was "renal death" (ESRD or death) in their latest version.[144] They found that relative risk of renal death was reduced by approximately 30% with the number-needed-to-treat ranging from 2 to 56, an acceptable range for recommended therapies.

Whether GFR is a sufficient outcome indicator for kidney disease in diet studies is open to question, even if measured by markers more reliable than serum creatinine. For example, the Modification of Diet in Renal Disease (MDRD) study failed to achieve its primary endpoint of reducing GFR loss (iothalamate clearance) in mostly nondiabetic persons with CKD of various degrees and causes.[145] Short-term GFR reduction was greater in the low protein group during the first 4 months presumably owing to lessened hyperfiltration. However, after 4 months, long-term GFR loss was actually slower in the low protein group. This biphasic GFR response precluded demonstrating a statistically significant difference overall between diet groups. Analyses of clinical endpoints provide stronger evidence than GFR measures for effects of therapeutic interventions. In a secondary analysis with extended follow-up (5 to 10 months after the intervention ended) in the MDRD study, lower protein intake reduced risk of ESRD or death (RR 0.63, 95% CI 0.38 to 1.02, p=0.056).[146] The MDRD study accrued relatively few clinical endpoints resulting in an underpowered analysis, but the direction of effect was consistent with benefit. Hansen and colleagues later performed a randomized, controlled clinical trial in patients with type 1 diabetes and stage 2 CKD.[147] A modest reduction from usual protein intake (mean 1.02 to 0.89 g/kg per day) decreased risk of ESRD and death by more than 50% (Figure 11-7). As in the MDRD study, a between-group difference in rate of GFR loss (^{51}Cr-EDTA clearance) was not detected.

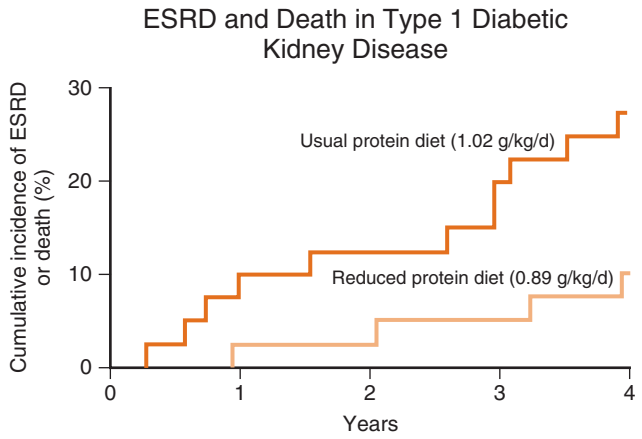


FIGURE 11-7 Cumulative incidence of ESRD or death by study group assignment to usual (1.02 g/kg/day) or reduced (0.89 g/kg/day) protein diet in type I diabetic kidney disease. Cox regression analysis adjusted for baseline presence of CVD, p = 0.01. (Adapted from H.P. Hansen, E. Tauber-Lassen, B.R. Jensen, et al., Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy, Kidney Int. 62 [2002] 220–228.)

In the present-day environment, "restriction" of dietary protein should actually be interpreted as avoidance of overeating. The National Health and Nutrition Examination Survey indicates that the majority of Americans consume about 15% of total daily calories or about 1.04 g/kg body weight per day as protein.[148] In fact, achieved intakes in "low protein" diet studies typically met or exceeded the Recommended Daily Allowance level of 0.8 g/kg per day. However, a truly low protein diet may lead to malnutrition, especially in patients with advanced CKD. Therefore, a sensible approach is to recommend that patients with diabetes and CKD aim for the Recommended Daily Allowance of dietary protein (approximately 0.8 g/kg/day or approximately 10% to 12% of calories) with an emphasis on high biological value foods (50% to 75% of protein intake) derived from poultry, fish, and plant-based sources. Dietary protein estimates based on body weight should be adjusted to idealized weight to prevent overestimating recommended intake levels due to obesity. Curbing dietary sources of advanced glycation end-products (AGE), which are metabolic mediators of kidney damage and CVD in diabetes, is also prudent in those with CKD.[149] The AGE load can be curtailed by consuming nonmeat proteins and by using culinary methods that reduce AGE formation.[150–152]

EMERGING ISSUES IN DIABETES AND CHRONIC KIDNEY DISEASE

Novel Therapies and Biomarkers

Despite the current standard-of-care for managing DKD, many patients have progressive kidney disease. Novel therapies, or possibly new uses of existing agents, are needed to advance care of DKD and related complications such as CVD and mortality.[153] Rigorous clinical trials are essential to novel therapy development. Epidemiological studies point

to valuable clues about disease causality and mechanisms, but must be considered hypothesis-generating studies. Similarly, observational studies from clinical trials conducted for other purposes are an important source of hypotheses, but they should not form the basis for clinical treatment decisions. On the other end of the spectrum, experimental models employing individual cells to whole animals are required to elucidate disease mechanisms and for early hypothesis testing. However, the human condition is extraordinarily more complex than experimental models can predict; thus, projections about therapeutic efficacy are often overly optimistic once clinical testing is conducted. Additionally, safety evaluation is essential because many new drugs will have unanticipated side effects for a myriad of reasons such as wrong doses or forms, metabolic interactions, or pleiotropic effects. Novel drug therapies in recent development for DKD are listed in Table 11-5.[153–156]

Availability of reliable biomarkers is paramount to development of novel therapies for DKD. At present, albuminuria and creatinine-based measures of GFR are the mainstays of biomarkers for most phase II studies. However, once the standard-of-care has been applied (e.g., renin-angiotensin system inhibition), albuminuria may already be influenced by this baseline treatment to a large extent, and consequently, it may not reliably predict clinical response to addition of other agents.[108] Additionally, DKD may be present without albuminuria.[157] Another open question that seemingly defies conventional logic is whether estimates of GFR based on creatinine (or other clearance markers) are sufficiently predictive of clinical endpoints such as death or ESRD. Ideally, biomarkers should reflect underlying disease mechanisms, prognosis, types of treatment indicated, and response to treatment. Application of rapidly advancing technologies in the areas of genomics, proteomics, and metabolomics should enable identification of new biomarkers not yet envisioned. These technologies also will facilitate vital lines of research for new DKD diagnostics and therapies. A list of promising potential biomarkers for DKD is provided in Table 11-6.

TABLE 11-6 Potential Biomarkers for Diabetic Kidney Disease

TYPE OR SOURCE	BIOMARKER
Advanced glycation end-products	• Carboxymethyllysine • Pentosidine
Growth factors	• Transforming growth factor-beta • Connective tissue growth factor
Oxidative stress	• Modified lipid products ◦ Malondialdehyde ◦ F2-isoprostanes • Modified DNA ◦ 2-deoxyguanosine
Discovery phase	
Genomics	• To be determined
Proteomics	• To be determined
Metabolomics	• To be determined

Multifactorial Risk Factor Management

Multiple risk factors are managed concurrently in patients with DKD, and the incremental effects of treating each of these risk factors appear to add up to substantial clinical benefits. At present, one of the best examples is the

TABLE 11-5 Novel Drug Therapies in Recent Development for Diabetic Kidney Disease

DRUG	STATUS
Sulodexide—Glycosaminoglycan and glomerular basement membrane restoration	Development was terminated for futility in reducing albuminuria.
Ruboxistaurin—Protein kinase C beta inhibitor	Phase 2 study reached primary endpoint of 25% albuminuria reduction. Further drug development is on-hold due to business and regulatory decisions.
• **Aminoguanidine**—Inhibitor of AGE formation	Development was terminated for uncertain efficacy and safety concerns (CVD events and vasculitis).
• **Pyridoxamine**—Inhibitor of AGE formation	Favorable phase 2 results obtained for safety and promising early data on efficacy for preservation of kidney function.
• **Alagebrium**—AGE cross-link breaker	Study terminated for undisclosed reason.
Antifibrotic treatments	
• **Perfinidone**	Phase 2 study has been completed, but not yet reported.
• **Anticonnective tissue growth factor antibody**	Phase 2 studies are in progress.
• **Antitransforming growth factor beta antibody**	Studies are planned.
• **Rhubarb extract**	Study is in progress.
Antioxidants	
• **Bardoxolone**	Study is in progress.
• **Benfotiamine**	Study is in progress.
Endothelin antagonists	
• **Avosentan**	Phase 2 study reported albuminuria reduction. Phase 3 study was subsequently halted for safety concerns (edema).
• **Bosentan**	Study is in progress.
Vitamin D	Study is in progress.

AGE, antiadvanced glycation end-products.
From ClinicalTrials.gov website accessed on March 13 and 22, 2009.

STENO-2 study, a randomized trial that investigated a multifaceted intensive intervention versus usual care in persons with type 2 diabetes and microalbuminuria. The intensive intervention had multiple targets including behavioral modification and pharmacological therapies for hyperglycemia, hypertension (emphasizing renin angiotensin system inhibitors), dyslipidemia, aspirin, and vitamin and mineral supplementation. For the behavioral modification component, patients were encouraged to adopt healthy lifestyles that included proper nutrition, regular exercise, and smoking cessation.[158]

Compared to usual care, patients receiving the intensive intervention had significantly larger mean decreases in systolic blood pressure (11 mmHg), diastolic blood pressure (4 mmHg), fasting plasma glucose (34 mg/dl), glycosylated hemoglobin (0.7%), triglycerides (50 mg/dl), total cholesterol (47 mg/dl), and LDL cholesterol (34 mg/dl).[157] These changes corresponded to a mean reduction of albuminuria (20 mg/24 hrs) for the intensive intervention, whereas there was a mean increase in patients receiving usual care (30 mg/24 hrs) The intensive intervention reduced albuminuria progression, retinopathy, neuropathy, and a composite outcome of CVD events or death.[159] Other interventions using some of the individual components (aspirin, vitamin C, or vitamin E) did not reduce albuminuria in smaller, short-term studies.[160,161] Furthermore, vitamin E did not prevent development or progression of albuminuria or reduce CVD or mortality in a large, long-term study of patients with type II diabetes.[162]

After a mean treatment period of 7.8 years in the STENO-2 study, participants were subsequently followed observationally for an average of another 5.5 years. Only one patient in the intensive treatment group had progression to ESRD, as compared to 6 patients in the conventional group ($p = 0.04$), whereas 20 patients in the intensive group developed DKD (defined as overt proteinuria) compared to 37 patients in the conventional group (RR 0.44, 95% CI, 0.25 to 0.77; $p = 0.004$). A time-to-first-event analysis for the primary CVD endpoint (composite of CVD death, nonfatal MI, nonfatal stroke, revascularization procedures, amputation) showed that the adjusted hazard ratio for an endpoint in the intensive intervention group was 0.47 (95% CI 0.22-0.74, $p=0.01$). An impressive 20% absolute risk reduction for the primary CVD endpoint was obtained with this intensive intervention strategy. Moreover, the survival curves for the primary endpoint in the two groups showed divergence as early as 24 months and continued to separate until the end of follow-up.[163]

Special Populations

The increasing incidence of diabetes in children, adolescents, young adults, the elderly, and members of disadvantaged and transitional populations is responsible for an escalating incidence of DKD among these groups. Therefore, screening and interventions should be focused on such high-risk populations. Although management strategies for DKD in special populations follow the same principles as in the majority population, there are special considerations in the treatment of children, adolescents, and the elderly. Children and the elderly within these populations appear to be at particularly high risk for DKD complications.[164,165] Additionally, the number of young women with diabetes who may become pregnant and already have DKD is rising, yet little is known about the effects on these women or on their offspring.

Racial and Ethnic Minorities

In the United States, the burden of DKD is borne disproportionately by ethnic and racial minorities. Disparities in the incidence of ESRD due to diabetes among ethnic groups have existed for many years, but the magnitude of these disparities has recently increased. For example, incidence rates are about four times higher among African Americans and American Indians than among whites.[4] Although recent data from the United States Renal Data System have suggested a plateau in overall incidence of ESRD attributed to diabetes, not all ethnic groups show this trend. African Americans and American Indians have a rapidly rising incidence of ESRD due to diabetes in the 30- to 39-year-old age range (see Figure 11-1). Racial minorities appear to have greater risk and more rapid progression of DKD, which may be related to earlier age at onset of diabetes, diet, exercise patterns, living conditions, access to medical care, education, infections, environmental toxins, and genetic susceptibility.[165–170] Moreover, as the population of people with diabetes grows worldwide, reports of a dramatically rising burden of DKD are now appearing from Africa, India, Pacific Islands, and Asia.[171–176] Increased risk and more rapid progression of DKD have also been reported in immigrants to Europe from South Asia.[177–180]

Children and Adolescents

The widespread increase in childhood obesity has lead to an expanding prevalence of type 2 diabetes among children and adolescents.[181] Although pediatric populations throughout the United States have shown dramatic increases in the prevalence of obesity (>10% in 2- to 5-year-old children and >15% in 6- to 19-year-old children), the greatest increases have occurred in racial minorities.[182] At the same time, there has been a global increase in type 1 diabetes, particularly among children younger than 5-years-old.[183] Given that duration of diabetes, rather than the age of onset, is the more predominant risk factor for DKD, higher rates of both types of diabetes in children and adolescents will likely lead to an increase in DKD by late adolescence and early adulthood, which is a finding that has already been documented in American Indians.[164,184] Optimal treatment of diabetes in the young is essential to reduce the burden of future DKD. Public health interventions that promote healthy diet and exercise may offer a unique opportunity to preempt DKD by preventing obesity and type 2 diabetes in the first place.[185]

Young people with DKD pose a number of unique concerns. Data regarding treatment of hyperglycemia, hypertension, and dyslipidemia in diabetic children or adolescents with kidney disease are almost nonexistent. However, therapeutic lifestyle changes (diet, exercise, and weight loss, when appropriate) are prudent for these risk factors. Given the higher risk of hypoglycemia in patients with decreased

kidney function, treatment goals must be carefully individualized. In children or adolescents with type 2 diabetes, therapeutic lifestyle changes should be the initial interventions for hyperglycemia.[9,186] If lifestyle changes do not succeed in achieving the target for glycemic control (HbA1c <7%), then drug therapy should be initiated. Although the ADA recommends oral agents as first-line therapy for children or adolescents with type 2 diabetes, only metformin is FDA-approved for this use, and it is only approved in children older than 10-years-old.[9] However, metformin should be avoided in children and adolescents with diabetes and decreased kidney function. Cautions regarding the use of other oral agents in children and adolescents with DKD are the same as those described for adults with the exception that thiazolidinediones should not be used because of concerns about liver toxicity due to the early experience with troglitazone.

KDOQI recommends a target blood pressure less than the 90th percentile for age, sex, and height or less than 130/80 mmHg, whichever is lower, for children and adolescents with DKD.[1,9] Although not approved for use by the FDA, both the NKF and the ADA suggest that ACE inhibitors are the drugs of choice for treatment of hypertension in children and adolescents with DKD.[39,41] ARBs are reasonable alternatives if ACE inhibitors are not tolerated. Adolescent girls must be counseled about pregnancy prevention while on ACE inhibitors or ARBs and about immediate discontinuation of these agents should pregnancy be suspected.

Drug therapy should be considered for severe hypertriglyceridemia (triglycerides >500 mg/dl) or marked elevations in LDL cholesterol (>160 mg/dl) that are unresponsive to control of hyperglycemia or therapeutic lifestyle changes according to the KDOQI Guidelines on Managing Dyslipidemias in Chronic Kidney Disease.[116] Fibric acid derivatives are preferred for hypertriglyceridemia treatment, but are not FDA-approved for use in children or adolescents. Statins are preferred agents for elevated LDL cholesterol, and atorvastatin received FDA approval for use in children and adolescents with familial hypercholesterolemia. The ADA Standards of Medical Care suggest an LDL cholesterol target of less than 100 mg/dl in diabetic children and adolescents.[9] Adolescent girls must be counseled about pregnancy prevention while on statins and about immediate discontinuation of these agents should pregnancy be suspected.

Children and adolescents should be referred to a registered dietitian who is experienced in managing DKD in this age group. For those who are obese, weight loss strategies should include both increased physical activity and a well-balanced diet. High-protein diets (more than 20% of calories) should be avoided in children and adolescents with DKD. Conversely, low-protein diets (less than 10% of calories) should be avoided to ensure adequate nutrition for growth and development.

The Elderly

Elderly persons with DKD characteristically have a number of comorbidities, particularly cognitive and functional impairments along with CVD. The higher frequency of comorbid conditions in the elderly with diabetes may contribute to a higher prevalence of albuminuria. The appearance of albuminuria is less likely to predict progression of kidney disease, even in those with diabetes of long duration.[187] Instead, low eGFR may be a better marker of progressive DKD than albuminuria in older people.[188] Development of DKD predicts mortality and poor outcomes in association with nonadherence to medical regimens in the elderly.[189,190]

Benefits of intensive risk factor management should be judiciously considered in light of these attendant risks. Because hypoglycemia and hypotension are particular concerns, less intensive goals should be considered. Drug therapies for hyperglycemia, hypertension, and dyslipidemia can be used as for others with DKD. However, drugs should be started at low doses and carefully titrated to monitor for responses and side-effects.

Pregnant Women

Due to the increasing prevalence of type 2 diabetes in the young, women may become pregnant after development of DKD. Microalbuminuria in women who are pregnant and have type 1 diabetes increases risks of adverse maternal and child outcomes including preeclampsia and preterm delivery.[191] Macroalbuminuria further increases these risks and may also increase the risk of perinatal mortality.[192] Macroalbuminuria also appears to increase the risks for preterm birth, small-for-gestational-age infants, and perinatal mortality independent of preeclampsia.[193,194] Only a few studies have explored the progression of DKD in pregnant women.[195–198] Worsening of kidney disease has been most apparent in women who already had increased levels of serum creatinine and albuminuria at pregnancy onset. These women are likely to have a decline in kidney function during pregnancy and a higher risk of DKD progression after delivery.

KDOQI guidelines and recommendations regarding management of hypertension, hyperglycemia, dyslipidemia, and nutrition in women who are pregnant and have diabetes and CKD are outlined in Table 11-7.[1] ACE inhibitors and ARBs are known to have adverse effects on the fetus during the second and third trimesters, including acute kidney failure in neonates, lung toxicity, and skull hypoplasia. Newer evidence suggests that fetal abnormalities (malformations of the cardiovascular system, central nervous system, and kidney) during ACE-inhibitor treatment extend to the first trimester.[199] Renin-angiotensin system inhibitors should be discontinued immediately after a missed menstrual period or a positive pregnancy test in women with diabetes. Women and adolescent girls with childbearing potential who are treated with renin-angiotensin system inhibitors should be counseled about these risks.

Treatment of hypertension should follow the guidelines adopted by the American College of Obstetrics and Gynecology.[200] Because antihypertensive therapy does not reduce the risk of preeclampsia and may cause potential harm to the fetus, hypertension should be treated cautiously. Based on extensive experience, methyldopa has long been considered the drug of choice. Labetalol is now also considered a preferred agent because combined alpha- and beta-blockade may better preserve uterine perfusion. Beta-blockers are considered reasonable add-on or alternative therapies. However, some data suggest that atenolol early in pregnancy may cause fetal growth retardation. Long-acting calcium channel blockers or hydralazine are also considered reasonable add-on therapy. Diuretics are usually avoided in pregnancy, particularly when there are concerns about preeclampsia.

TABLE 11-7 Management of Risk Factors for CKD and CVD and Nutrition in Pregnant Women with Diabetes and CKD

RISK FACTOR	TREATMENT	GOAL	CAUTIONS
Hypertension	*Preferred:* Methyldopa Labetalol *Add-on drugs:* Hydralazine Long-acting calcium channel blockers	Treat if blood pressure greater than 140-160/90-105 mmHg Target blood pressure undetermined Consider target of less than 130/80 mmHg because of CKD. Avoid hypotension.	Stop ACE inhibitors and ARBs after first missed menstrual period or positive pregnancy test. Atenolol may cause fetal growth retardation in first trimester. Avoid diuretics unless given for hypertension preconception and no evidence of preeclampsia. If diuretic is continued during pregnancy, dose should be reduced.
Hyperglycemia	Insulin	HbA1c as close to normal as possible (<1% above upper limit of normal)	Excessive hypoglycemia
Hyperlipidemia	None		Stop statins and other lipid-lowering drugs after first missed menstrual period or positive pregnancy test.
Nutrition	Liberalize dietary protein to 1.0-1.2 g/kg (preconception weight) per day		

(Adapted from National Kidney Foundation—Kidney Disease Outcomes Quality Initiative [NKF-KDOQI], Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease, Am. J. Kidney Dis. 49 [2007] S1-S179; and American Diabetes Association, Standards of medical care in diabetes—2009, Diabetes Care 32 [2009] S13-S61.)

However, if a pregnant woman with chronic hypertension has been treated with a diuretic before conception, it is not necessary to discontinue therapy as long as there are no signs of preeclampsia. Nevertheless, reducing the diuretic dose with careful patient monitoring is recommended.[201]

Oral medicines have successfully controlled hyperglycemia in women with type 2 diabetes during pregnancy, but these studies did not include patients with CKD.[202,203] Therefore, the KDOQI guidelines indicate that insulin remains the pharmacological treatment of choice for hyperglycemia during pregnancy in women with diabetes and CKD, and goals for glycemic control should be the same as those for women without CKD.[1]

Pharmacological treatment of dyslipidemia during pregnancy is not currently recommended due to potential risks to the fetus.[1] Statins and other lipid-lowering therapies should be discontinued after a missed menstrual period or a positive pregnancy test in diabetic women with CKD. Women and adolescent girls with childbearing potential who are treated with lipid-lowering therapies should be counseled about these risks.

Dietary protein intake for women with diabetes and CKD should be liberalized during pregnancy to ensure adequate nutrition for the mother and fetus. The KDOQI guidelines and recommendations suggest that these patients should be counseled to increase their intake of protein to 1 to 1.2 g/kg per day based on idealized prepregnancy weight.

A full list of references are available at www.expertconsult.com.

Chapter 12

NUTRITION AND METABOLISM IN KIDNEY DISEASE

Alp Ikizler, M.D., and Lara B. Pupim, M.D., M.S.C.I.

Despite substantial improvements in the science and technology over the past decades, morbidity and mortality of patients with chronic kidney disease (CKD) remain high.[1] Among the many factors that affect outcome in this patient population, a state of metabolic and nutritional derangements, more aptly called *protein-energy wasting (PEW) of CKD*, plays a major role.[2] Multiple studies now indicate that these derangements are closely associated with important clinical outcomes such as hospitalization and death rates in CKD patients. The focus of this chapter is to review the current state of knowledge in the field of nutrition and metabolism in all stages of CKD. Because the prevalence and mechanisms of nutritional and metabolic derangements may be different for each stage of CKD, we will separately discuss each stage of CKD and renal replacement therapy (RRT) options, including kidney transplant as applicable.

NUTRIENT METABOLISM IN KIDNEY DISEASE

Protein Metabolism

For healthy adults consuming western diets, the protein intake usually exceeds the requirement. Despite an excess consumption of dietary protein, muscle mass does not always increase. Instead, the body adapts by oxidizing any excess of amino acids from dietary protein. The nitrogen liberated by amino acid oxidation is converted to waste nitrogen (principally urea) and is excreted by the kidney. When the intake of protein decreases, amino acid oxidation is reduced, which allows amino acids to be recycled and yields more efficient use of dietary essential amino acids (EAA).[3] In addition to amino acid oxidation, protein synthesis and degradation determine the net protein and nitrogen balance; approximately 280 grams of body protein are synthesized and degraded in a 70-kg adult each day. During fasting, body protein stores (principally skeletal muscle) undergo degradation to amino acids, which are used in the liver for gluconeogenesis. With feeding, protein degradation declines and protein synthesis either replenishes body protein stores or protein stores will be preserved as long as the diet is nutritionally adequate.

In CKD patients, the same principal of maintaining neutral nitrogen balance and preventing loss of protein mass is also applicable. Accordingly, the minimal daily protein intake of approximately 0.6 g/kg, the amount required in

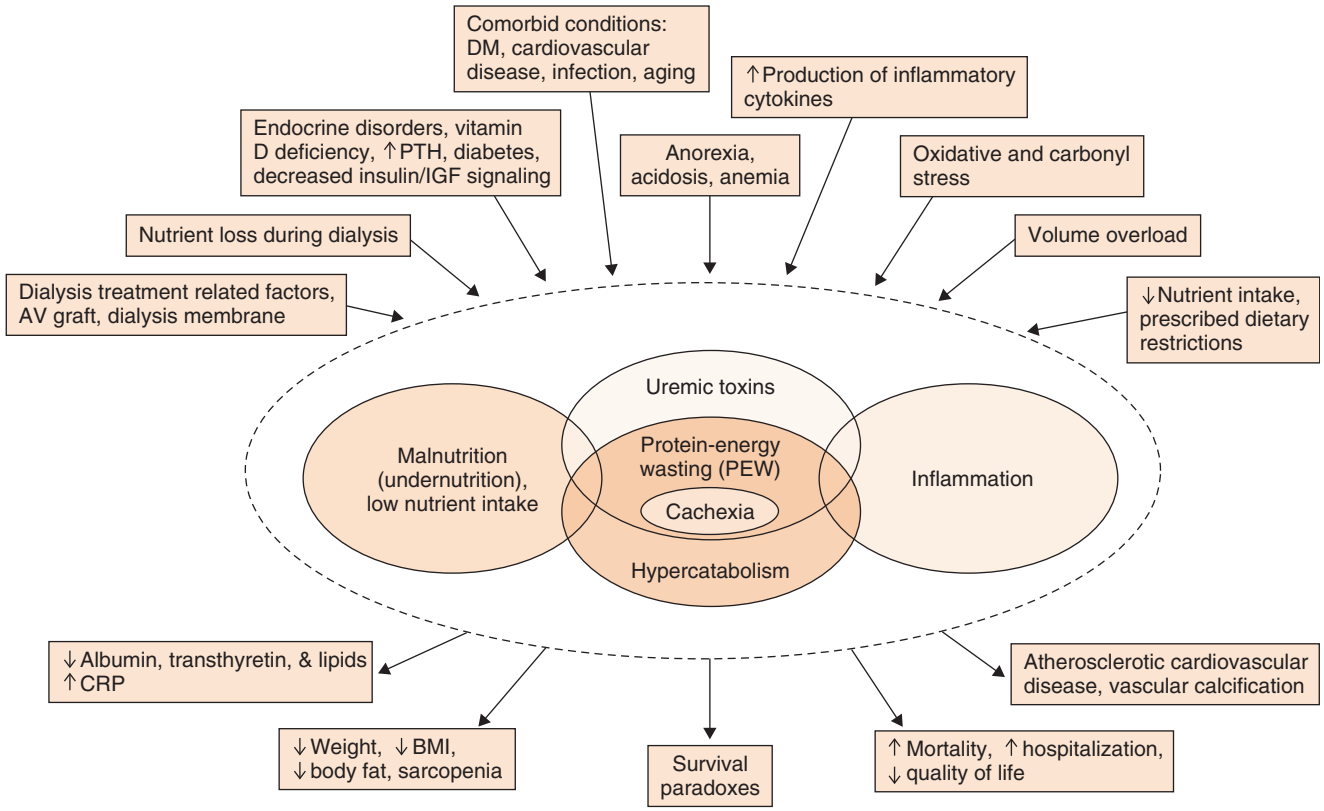


FIGURE 12-1 Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease. (From D. Fouque, K. Kalantar-Zadeh, J. Kopple, N. Cano, et al., A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease, Kidney Int. 73 [2008] 391-398.)

healthy individuals, is considered to be appropriate in stable CKD patients who are not yet initiated in renal replacement therapy. A safe level of protein intake is equivalent to the minimal requirement plus two standard deviations, or approximately 0.75 g/kg/day. In other words, more than 95% of healthy individuals and clinically stable CKD patients can maintain their protein stores over a prolonged period with this level of dietary protein intake.

One of the most significant findings of advanced kidney disease is a decrease in appetite, especially toward meat and meat products. Accordingly, CKD patients are known to spontaneously restrict their dietary protein intake with levels less than 0.6 g/kg/day when glomerular filtration rate (GFR) is less than 10 ml/min.[4] Furthermore, CKD patients encounter further catabolic stresses once they are initiated on maintenance dialysis therapy (Figure 12-1). These observations have led the nephrology community to believe that advanced CKD, or commonly termed "uremia," is a net protein catabolic state.[5,6] However, Lim and Kopple suggested that CKD, even when advanced, does not engender net protein breakdown.[7] They based this conclusion on nitrogen balance studies and whole body amino acid turnover kinetic studies by Goodship and colleagues and Lim and colleagues, which showed that there is a concomitant decrease in both protein synthesis and degradation in patients with advanced uremia, resulting in a net nitrogen balance no different from matched healthy controls, albeit at a significantly low protein turnover rate.[8,9] Similarly, Adey and colleagues showed no significant difference in whole-body net protein turnover in CKD patients compared to healthy controls.[10] They also reported that although whole-body leucine turnover is similar to healthy individuals, there was a significantly reduced fractional synthetic rate of several muscle proteins. In support of these findings, in an editorial Lim and colleagues proposed that there is dissociation between visceral protein and muscle protein turnover rates, especially during catabolic states such as hemodialysis and potentially advanced CKD.[11] It is likely that this is a physiologically expected adaptation as the rate of protein turnover is directly related to the production of certain end-products known as uremic toxins that accumulate in advanced CKD.

Overall, these observations indicate that advanced uremia leads to a syndrome of metabolic abnormalities that result in a low protein turnover state, but not necessarily with significant impact on net whole-body protein balance. A decreased dietary protein and energy intake, regardless of the cause (i.e., anorexia of uremia or prescription of low dietary protein intake) can be compensated for with an adjustment in the protein degradation with no significant impact on net balance. Therefore, clinically stable CKD patients are able to preserve their protein stores throughout the progression of renal disease, even in the setting of decreased dietary protein intake. However, the net gain or loss of cell and tissue protein in humans is ultimately determined by a balance between two opposite but complementary processes, protein synthesis and protein degradation. At times of accelerated protein degradation due to increased metabolic needs, such as acute illnesses or stress conditions, it is possible that patients with advanced uremia cannot initiate the appropriate compensatory mechanisms, such as increased protein synthesis. In the presence of inadequate dietary protein intake, it is likely that the synthetic capability will be insufficient as well. The lack of response to a catabolic stimulus

can also be a result of a defect in incorporation of the available nutrients inherent to uremia or concurrent illnesses. Therefore, it is conceivable that low protein and energy intake can indirectly lead to the development of PEW in advanced CKD patients.[12] The recommended dietary protein intake level of 0.6 to 0.8 g/kg/day is safe for stable CKD patients who are not yet on maintenance dialysis but should be raised to accommodate the increased metabolic needs of patients with ongoing catabolic processes.

Accumulation of uremic toxins may not be the sole cause of decreased dietary nutrient intake. Figure 12-1 depicts some of the factors that can cause decreased nutrient intake, especially protein intake in chronic kidney disease patients. Patients with kidney disease secondary to diabetes mellitus are more prone to nutritional derangements because of dietary restrictions and gastrointestinal symptoms such as gastroparesis, nausea, and vomiting, and bacterial overgrowth in the gut and pancreatic insufficiency. Patients with diabetic CKD with poorly controlled blood sugar tend to have increased protein breakdown. Depression, which is commonly seen in CKD patients, is also associated with anorexia. In addition, CKD patients are usually prescribed a large number of medications, particularly sedatives, phosphate binders, and iron supplements, which are also associated with gastrointestinal complications. Finally, the socioeconomic status of the CKD patients, and their lack of mobility, and their age are other predisposing factors for decreased dietary protein intake.

Several renal replacement therapy related factors predispose advanced CKD patients to negative nitrogen balance. There are inevitable losses of amino acids during both hemodialysis (HD) and peritoneal dialysis (PD), ranging from 5 to 8 grams of amino acids per HD session and 5 to 12 g/day of amino acids during PD. Losses may be higher with high efficiency HD or when peritonitis is present. The absorption of glucose during PD may also predispose patients to anorexia due to the development of satiety. In addition, a feeling of fullness may be related to the fluid in the peritoneal cavity. One of the most important factors affecting the nutritional status of dialysis patients is the dose of dialysis. The amount of dialysis should be adequate to prevent development of PEW in both HD and PD patients.

The previously mentioned aspects of CKD lead to well-defined abnormalities in plasma and to a lesser extent in muscle amino acid profiles. Commonly, essential amino acid concentrations are low and nonessential amino acid concentrations are high. The etiology of this abnormal profile is multifactorial. The progressive loss of kidney tissue, which is where metabolism of several amino acids takes place, is an important factor. Specifically, glycine and phenylalanine concentrations are elevated, and serine, tyrosine, and histidine concentrations are decreased. Plasma and muscle concentrations of branched-chain amino acids (valine, leucine, and isoleucine) are reduced in chronic dialysis patients. Among these, valine displays the greatest reduction. In contrast, plasma citrulline, cystine, aspartate, methionine, and both 1- and 3-methylhistidine levels are increased. Although inadequate dietary intake is a possible factor in abnormal essential amino acid profiles, certain abnormalities occur even in the presence of adequate dietary nutrient intake, indicating that the uremic milieu has an additional effect. Indeed, it has been suggested that the metabolic acidosis that is commonly seen in advanced CKD patients plays an important role in increased oxidation of branched-chain amino acids.

Carbohydrate Metabolism

Disorders of carbohydrate metabolism are frequent in CKD patients. Diabetic nephropathy accounts for more than 40% of end-stage renal disease (ESRD) in the United States, and more than 60% of the ESRD patients carry a diagnosis of diabetes mellitus (DM). Furthermore, nondiabetic CKD patients often have glucose intolerance, mostly because of peripheral insulin resistance (IR). Accordingly, reduced insulin-mediated nonoxidative glucose disposal is the most evident defect of glucose metabolism, but impairments of glucose oxidation, the defective suppression of endogenous glucose production, and abnormal insulin secretion also contribute to glucose intolerance observed in CKD patients.[13]

The etiology of IR in CKD is multifactorial with likely contributions from vitamin D deficiency, obesity, metabolic acidosis, inflammation, and accumulation of "uremic toxins" that lead to acquired defects in the insulin-receptor signaling pathway. An important consequence in ESRD is its role in the pathogenesis of uremic protein energy wasting. In the general population, insulin resistance has been associated with accelerated protein catabolism. Among patients with ESRD, enhanced muscle protein breakdown has been observed in patients with type II DM compared to patients with ESRD without DM.[14] In the absence of DM or severe obesity, insulin resistance is detectable in dialysis patients and is strongly associated with increased muscle protein breakdown, even after controlling for inflammation.[15] This process appears to be mediated by the ubiquitin-proteasome pathway.

Lipid Metabolism

Dyslipidemia is quite common in CKD patients, and abnormalities in lipid profiles can be detected in patients once kidney function begins to deteriorate, which suggests that progressive loss of kidney function is associated with lipid disorders. The presence of nephrotic syndrome or other comorbidities such as DM and liver disease, and the use of medications altering lipid metabolism (e.g., thiazide diuretics, beta blockers), further contribute to the dyslipidemia seen in CKD.

In hemodialysis patients, the most common abnormalities are elevated serum triglycerides and very-low-density lipoproteins, and decreased low-density lipoproteins (LDL) and high-density lipoproteins (HDL).[16] The increased triglyceride component is thought to be related to increased levels of apolipoprotein CIII, which is an inhibitor of lipoprotein lipase. A substantial number of maintenance hemodialysis (MHD) patients also have elevated lipoprotein (a) levels. Patients on PD exhibit higher concentrations of serum cholesterol, triglyceride, LDL cholesterol, and apolipoprotein B, even though the mechanisms that alter the lipid metabolism are similar to CHD patients.[17] This is thought to be related to increased protein losses through the

peritoneum, possibly by mechanisms that are operative in the nephrotic syndrome and the glucose load supplied by dialysate causing increased triglyceride synthesis and hyperinsulinemia. They also exhibit higher concentrations of lipoprotein (a). Whether these differences in lipid profiles are clinically significant remains to be clarified.

Vitamins

Patients with CKD, especially those with advanced stages such as 3 to 5, are prone to a high incidence of vitamin deficiencies if they do not receive supplements. Table 12-1 shows commonly recognized abnormalities in vitamins in patients with CKD. Deficiencies in vitamins are due to several factors including impaired production, decreased intake due to anorexia, concurrent illnesses, and dietary restrictions related to CKD.[18] Specifically, diets prescribed for moderate and advanced CKD frequently contain less than the recommended daily allowances for certain water-soluble vitamins. Finally, the absorption, metabolism, or activity of some vitamins such as riboflavin, folate, pyridoxine, and vitamin D3 are altered in CKD, either due to impaired intestinal activity or interferences of absorption due to certain medicines. Although patients with stage 1 and 2 CKD are less likely to suffer from vitamin deficiencies, a substantial proportion of patients with stage 3 or 4 CKD appear to develop laboratory evidence for one or more vitamin deficiencies. Accordingly, a specialized supplemental intake of multivitamins in addition to the vitamins that are ingested with foods is recommended in patients with stage 3 to 5 CKD (see Table 12-1). There is no indication that patients with stage 1 and 2 CKD require any supplemental vitamins with the exception of patients with nephrotic syndrome.

TABLE 12-1 Commonly Recognized Abnormalities in Vitamins in Patients With Chronic Kidney Disease Who are Not on Any Vitamin Supplementation and Recommended Daily Supplemental Vitamins in Addition to the Patient's Daily Intake of Vitamins from Foods Ingested for Individuals with Stages 3 to 5 Chronic Kidney Disease (Who are Not on Dialysis). There is no Additional Supplementation Recommendation for Patients with Stage 1 and 2 CKD, Except Patients with Nephrotic Syndrome.

VITAMIN	SERUM OR PLASMA CONCENTRATIONS IN CHRONIC KIDNEY DISEASE	RECOMMENDED DOSE STAGE 3-5 CKD
Thiamin	Decreased or normal	1.2 mg/day
Riboflavin	Decreased or normal	1.3 mg/day
Pyridoxine	Decreased or normal in serum, decreased in RBC	5 mg/day
Cobalamin	Increased	None
Folic acid	Decreased or normal in serum and increased or normal in RBC	1 mg/day
Ascorbic acid	Decreased or normal	60 mg/day
Vitamin A	Increased in serum	No addition (avoid in CKD 3-5)
Vitamin E	Decreased, increased, or normal	15 mg/day
Vitamin D	Decreased	See Chapter 9
Vitamin K	Decreased or normal	None*
Vitamin B12	Decreased or normal	2.4 mcg/day
Niacin	Decreased† or normal	14-16 mg/day
Pantothenic acid	Decreased,† increased,‡ or normal	5 mg/day

Serum levels of many trace elements and vitamins may be reduced in the nephrotic syndrome because of increased urinary losses and low serum levels of binding proteins. The recommended daily requirements for normal adults may vary according to gender and age group in adults. The table reflects the highest recommended level for nonpregnant, nonlactating adults.
*May need to be supplemented in severely malnourished patients.
†Decreased in CKD patients on low-protein diets.
‡Increased in maintenance hemodialysis patients.
RBC, erythrocytes.

Trace Elements

The term "trace element" was initially developed to identify all elements in body fluids and tissues that occur in such extremely small amounts that they could not be measured accurately, although almost all of them can be measured with extreme precision with the available methodologies. There is an exhaustive list of trace elements, and the significance of most of these elements in kidney disease is not established.[18] It is generally believed that the body burden and tissue concentrations of many trace elements are altered in CKD and ESRD. Some of the trace element concentrations rise with kidney disease, whereas some show a tendency to decrease. Various factors contribute to these alterations, including but not limited to decreased clearance by the kidneys, excessive quantities with urinary protein losses as in nephrotic syndrome, inadequate intake due to anorexia, and decreased absorption due to renal failure or other coexisting gastrointestinal problems. Dietary requirements for trace elements have not been defined for CKD patients because of the difficulties in conducting the studies to determine nutritional requirements.

ASSESSMENT OF NUTRITIONAL STATUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

A great variety of nutritional parameters have been used in the many studies designed to detect PEW in patients with CKD. The International Society of Renal Nutrition and Metabolism organized an expert panel to reexamine the terms and criteria used for the diagnosis of PEW.[19] A summary of these parameters and their applicability for guiding nutritional therapies based on this expert panel report is provided in Table 12-2.

Patient Interview

Symptoms of nausea, vomiting, and anorexia, and recent changes in body weight, should be carefully evaluated to ascertain the cause. Non-CKD etiologies must be kept in mind, including severe congestive heart failure, diabetes, various gastrointestinal diseases, and depression. Phosphate binders or oral iron preparations can cause dyspepsia, and prednisone can increase the protein catabolic rate.

TABLE 12-2 Suggested Table to Monitor Nutritional Status and Guide Therapy in Kidney Failure

SIMPLE (MONTHLY) ASSESSMENT	FINDINGS	POSSIBLE INTERVENTIONS
BW	Continuous decline or < 85% IBW	Suspect of uremic malnutrition and perform more detailed nutritional assessment
Serum albumin	< 4.0 g/dl	No intervention needed at this point
Serum creatinine	Relatively low pre-dialysis values	
DETAILED ASSESSMENT	**FINDINGS**	**POSSIBLE INTERVENTIONS (SIMPLE)**
Serum prealbumin	< 30 mg/dl, and/or	Dietary counseling: DPI ≥ 1.2 g/kg/d, energy intake 30-35 kcal/d
Serum transferrin	< 200 mg/dl, and/or	*CHD and PD*
	< 200 ng/ml, and/or	Increase dialysis dose to Kt/V > 1.4
IGF-I LBM and/or fat mass	Unexpected decrease	Use biocompatible membranes
SGA	Worsening	Upper GI motility enhancer
		CKD
		Consider timely initiation of CDT
REPEAT DETAILED ASSESSMENT (2 TO 3 MONTHS FROM PREVIOUS)	**FINDINGS**	**POSSIBLE INTERVENTIONS (MODERATE TO COMPLEX)**
Serum prealbumin	< 30 mg/dl, and/or	*Nutritional supplements:*
Serum transferrin	< 200 mg/dl, and/or	Oral, enteric tube feeding, IDPN (requires Medicare approval)
IGF-I	< 200 ng/ml, and/or	*Anabolic factors (experimental):*
Serum creatinine	Relatively low predialysis values, and/or	rhGH, rhIGF-I
LBM and/or fat mass	Unexpected decrease	*Appetite stimulants (experimental)*
C-reactive protein	> 10 mg/L	*Antiinflammatory (experimental)*

(Adapted from L.B. Pupim, L. Cuppari , T.A. Ikizler, Nutrition and metabolism in kidney disease, Semin. Nephrol. 26 [2006] 134-157, with permission.)

Visceral Protein Stores

Serum albumin has been by far the most widely used nutritional marker in MHD patients. This is primarily due to its easy availability and strong association with hospitalization and death risk. Despite its reliable, albeit delayed, response to dietary interventions, there are many nonnutritional factors that directly influence serum albumin concentrations such as decreased synthesis due to hepatic diseases, increased transcapillary losses, increased losses through the gastrointestinal tract and kidneys, and tissue injuries such as wounds, burns, and peritonitis.[20] Furthermore, serum albumin levels have been shown to decrease in situations of volume overload, which is highly prevalent in MHD patients. Serum albumin, as a negative acute-phase reactant, is also affected by conditions such as inflammation, infection, and trauma, that lead to prompt and usually substantial decreases in its serum concentrations.[20] In this context, the decrease in serum albumin concentrations may more closely reflect the degree of illness and inflammation, rather than the overall nutritional status. Nonetheless, low levels of serum albumin are highly predictive of poor clinical outcomes in all stages of CKD; therefore, serum albumin is still considered a reliable marker of general nutritional status.

Among other potential nutritional biomarkers, serum transferrin is low in almost all MHD patients and is influenced by changes in iron stores, presence of inflammation, and changes in volume status; it is not a good indicator of nutritional status. Serum prealbumin levels may be elevated due to interaction of prealbumin with retinol-binding protein and decreased renal clearance. It is a negative acute phase reactant as well. C-reactive protein (CRP) is an acute phase reactant that correlates negatively with visceral protein concentrations. When serum levels of albumin or prealbumin are low, it is appropriate to check CRP levels to help uncover potential covert inflammation, although CRP levels are highly variable in CKD patients, reducing their practical use.[21] Some evidence does suggest serial CRP measurements are valuable, at least for complicated cases.[22]

Body Composition

The assessment of body composition and of somatic protein stores involves the measurement of different body compartments (water, fat, bone, muscle, and visceral organs). The fat-free mass (mainly composed of muscle) comprises the majority of the somatic protein mass. Generally, somatic protein stores are preserved at the expense of other body fuel sources, especially fat. However, when catabolic illnesses occur there will be fat-free mass depletion. Therefore, body composition techniques are important tools to diagnose protein depletion and to monitor efficacy of nutritional therapies. Simple anthropometric measures are practically useful whereas bioelectrical impedance analysis and dual-energy x-ray absorptiometry are more applicable for research purposes.

Dietary Intake

Estimation of energy and protein intake by different methods can also be used as a marker of overall nutritional status in patients with CKD. Although dietary diaries and history are direct and simple measures of dietary intake, several studies have shown that these methods lack accuracy in estimating the actual intake of patients, even in experimental settings.[23,24] Differently from energy intake, which can only be estimated by using less accurate methods, dietary protein intake (DPI) can be measured by other more reliable means, such as 24-hour urine urea nitrogen excretion in patients with CKD who are not yet on dialysis[25] or protein equivalent of total nitrogen appearance (PNA) in dialysis patients.

However, it should be noted that these indirect estimations of DPI are only valid in clinically stable patients, and they may easily overestimate the actual intake in catabolic patients, in whom endogenous protein breakdown may lead to a high urea nitrogen appearance.[26] Concerns have also been raised regarding whether PNA is mathematically linked to Kt/V rather than an independent nutritional parameter.[27] Although this question has not yet been elucidated, one study including adequately dialyzed hemodialysis patients (Kt/V > 1.2) showed that PNA correlates with hospitalization and mortality but not with Kt/V.[28] However, considering that there are still uncertainties regarding the relationship between PNA and nutritional status, PNA results should be analyzed with caution and in conjunction with other more reliable markers of PEW.

Composite Indices of Nutritional Status

These diagnostic measures take into account not only some of the body composition and dietary intake assessment tools but also must incorporate a degree of subjective assessment of overall nutritional status. The most commonly used composite indices include subjective global assessment (SGA) or modified or expanded indices that incorporate the SGA or its components, such as the composite nutritional index and the malnutrition-inflammation score (MIS). They are clinically useful tools for evaluating nutritional status from a broader perspective, including medical history, symptoms, and physical parameters.

SGA was originally used to predict outcomes in surgical patients with gastrointestinal disease, and it has been validated as a screening tool for this population.[29] On the basis of evaluation of history of weight changes, nutritional intake and gastrointestinal symptoms, nutrition-related functional impairment, and physical examination to assess subcutaneous fat, muscle stores, and the presence or absence of edema, patients are divided into three categories: A, well-nourished; B, mild to moderately malnourished; or C, severely malnourished. Although SGA was found to correlate with other measures of nutritional status in maintenance dialysis patients, it does not reliably detect sarcopenia (based on total body nitrogen).[30] Furthermore, SGA scores tend to discriminate well between best- versus worst-nourished patients but fail to separate out the mild or moderate PEW in MHD patient. It is recommended in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines that the modified SGA be performed every 6 months in MHD patients.[31] The subjective nature, lack of inclusion of measures of visceral protein stores, and relative insensitivity to small changes in nutritional status of SGA led others to create a more comprehensive nutritional index that includes the SGA and parameters based on body weight and weight-for-height, skinfold measures, and serum albumin concentration.

The MIS incorporates components of the SGA and includes other components related to nutritional status (body mass index), a combination of nutritional status and inflammation (serum albumin concentration and total iron binding capacity), and components not directly indicative of nutritional status, such as comorbidities and functional status.[32] The MIS is not as closely associated with measures of body composition as is the SGA. As with any method of nutritional status assessment, SGA, composite nutritional index, or MIS should be used in conjunction with other methods.

Monitoring the nutritional status on a regular basis is the key to early detection of nutritional disturbances in CKD patients to evaluate the response of nutritional interventions and to motivate and improve the patient's compliance to the dietary therapy. Although there is no definitive protocol for routine follow-up, body weight and normalized PNA (nPNA) should be monitored monthly. Serum albumin, prealbumin, and cholesterol should be determined every 3 months in clinically stable patients. Other anthropometric measurements, dietary interviews, and SGA should be obtained every 6 months or more often in those patients at risk of developing PEW and those patients with established PEW. Figure 12-2 depicts a proposed algorithm for the assessment and management of nutritional status in maintenance dialysis patients.

EPIDEMIOLOGY OF PROTEIN-ENERGY WASTING IN CHRONIC KIDNEY DISEASE PATIENTS

Patients with Chronic Kidney Disease

Data regarding the prevalence of inadequate nutritional status in CKD patients are limited when compared with that of patients commencing or already on chronic dialysis therapy. Although there is some evidence showing a worsening in the nutritional parameters with the progression of CKD,[33] PEW seems to be more evident in stage 5 CKD, especially in patients not previously submitted to dietary counseling.[34] In fact, the prevalence of PEW assessed by SGA was found to be of about 40% in patients with GFR lower than 15 ml/min.[35] In spite of a progressive decrease in DPI as kidney function deteriorates,[4] a number of studies indicate that CKD patients prescribed low-protein or even very-low-protein diets are able to maintain adequate nutritional status as CKD advances, provided that they are carefully monitored with regards to dietary intake and clinical conditions.[36,37] In the 2-year follow-up analysis of the Modification of Diet in Renal Disease (MDRD) study, a significant increase in serum albumin and only subtle reductions in anthropometric parameters were observed in a group of carefully monitored patients who were prescribed a low protein diet. There were only two withdrawals from the MDRD study because of deterioration of nutritional status.[37] However, the intense follow-up employed in the MDRD study cannot be easily performed in the real clinical setting.

Patients with End-Stage Renal Disease

Virtually every study evaluating the nutritional status of MHD patients report some degree of inadequate nutritional status in this population, particularly regarding protein and energy depletion. Due to the many different diagnostic tools used in separate studies, the prevalence of PEW in MHD patients varies widely among different reports, ranging from 20% to 60%.[38] However, there is evidence of improvement in nutritional parameters within 3 to 6 months following initiation of hemodialysis, and the prevalence seems to increase as the time on MHD extends.[39]

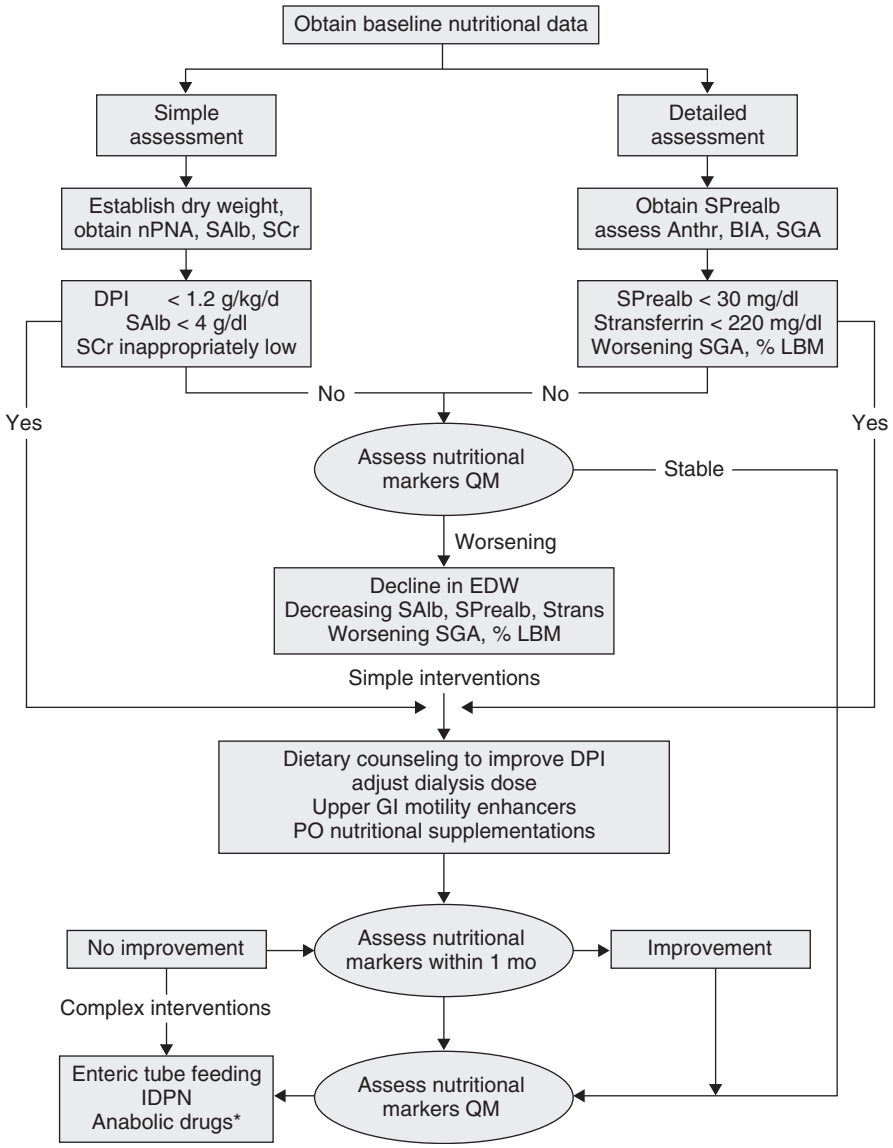


FIGURE 12-2 A proposed algorithm the assessment and management of nutritional status in MHD patients. *Anthr*, anthropometric measurements; *BIA*, bioelectrical impedance analysis; *DPI*, dietary protein intake; *EDW*, estimated dry weight; *GI*, gastrointestinal; *IDPN*, intradialytic parenteral nutrition; *LBM*, lean body mass; *nPNA*, normalized protein nitrogen appearance rate; *QM*, every month; *SAlb*, serum albumin; *SCr*, serum creatinine; *SGA*, subjective global assessment; *SPrealb*, serum prealbumin. *Mostly experimental.

Many epidemiological reports on nutrition in MHD patients have been based mainly on serum albumin concentrations. In the baseline phase of the Hemodialysis (HEMO) Study, 29% of the patients had albumin levels below 3.5 g/dl. Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest a lower prevalence of hypoalbuminemia in countries other than the United States such that the lowest mean serum albumin level was observed in the United Kingdom for Europe, whereas the United States' value was significantly lower than in all European countries (3.60 g/dl versus 3.72 g/dl [36 g/L versus 37 g/L]).[40] In a separate analysis, Japan had significantly higher albumin compared with the United States when adjusted for patient age, sex, and day of laboratory draw. In DOPPS II, 20.5% of U.S. patients had a serum albumin level less than 3.5 g/dl (35 g/L). Results from the DOPPS also showed a prevalence ranging from 7.6% (United States) to 18% (France) for moderately malnourished and 2.3% (Italy) to 11% (United States) for severely malnourished MHD patients as diagnosed by SGA and an average MIS score ranging from 5.8 in Japan to 10.7 in Germany, with scores ranging from 9 to 10.1 in United States, Italy, France, Japan and United Kingdom.[41]

The clinical relevance of the aforementioned data is that practically every nutritional marker used in MHD patients has been associated with hospitalization and death risk. These observations are reproducible irrespective of patient demographics and geographical area. Epidemiological data also indicate a survival benefit with improvement in these markers overtime.[42] This alleged benefit has been observed for serum albumin and body mass index.

FACTORS AFFECTING NUTRITIONAL STATUS IN CHRONIC KIDNEY DISEASE

Multiple factors play important roles in the development of PEW, many of which act concurrently. In the following pages, we provide a review of studies on these factors as they

pertain to CKD and RRT, including kidney transplant, as applicable. Nonetheless, most of these factors may overlap between the various stages and therapies of CKD while others may persist through all stages of CKD.

Poor Dietary Nutrient Intake

Anorexia, as evidenced by decreased dietary protein and energy intake, is a hallmark of advanced CKD.[43] Studies have shown that dietary nutrient intake decreases as a result of worsening kidney function, and they emphasize the adverse effects of decreased food intake on nutritional status.[33,37,44] An early cross-sectional study of 900 CKD patients reported spontaneous decreases in food intake, specifically of high-protein products, with decreasing kidney function.[45] Likewise, the MDRD study suggested a positive correlation between the GFR and the actual and reported protein and energy intake, that is, the lower the GFR, the lower was the protein and energy intake.[46,47] The authors suggested that the signs of protein and energy depletion become more evident when the GFR is less than 10 ml/min. Similarly, in a prospective analysis of protein intake by patients with progressive CKD but with minimal dietary interventions, many patients spontaneously restricted their protein intake with progression of kidney disease, with DPI less than 0.6 g/kg/day when creatinine clearance was less than 10 ml/min.[4] In this study, it was reported that other markers of nutrition such as weight and Insulin-like Growth Factor I (IGF I) concentrations correlated with kidney function and protein intake. Duenhas and colleagues examined spontaneous food intake and nutritional parameters in 487 patients with different degrees of CKD without dietary interventions. They found that both energy and protein (nPNA) intakes were significantly lower in patients in the lower quartile of creatinine clearance (<19.9 ml/min/1.73 m^2) compared to the highest quartile (>43 ml/min/1.73 m^2).[48] In this study, other nutritional parameters such as body mass index, percent of ideal body weight, percent of midarm muscle circumference, and percent of triceps skinfold thickness were also significantly lower in the lowest quartile when compared to the highest quartile of creatinine clearance.

While the exact mechanism by which uremia leads to anorexia has not been elucidated, a landmark study by Bergstrom and colleagues demonstrated that accumulation of a low molecular weight substance (<5 Kd) that was isolated from uremic plasma ultrafiltrate and normal urine and injected in otherwise healthy rats induced a dose-dependent suppression of appetite.[6] Although a cause-and-effect relationship cannot be readily extrapolated to humans, these findings suggest that a relationship exists between the extent of kidney disease, as assessed by uremic toxin accumulation, and spontaneous dietary protein and energy intake and nutritional status.

Evidently these observations do not apply to patients who may be prescribed protein restricted diets, supplemented or not with essential amino acids and/or their ketoanalogs. Several studies, including the MDRD study, have shown that with close supervision and a heavy emphasis on energy intake, patients may have protein restricted diets without the development of overt malnutrition.[49–51] This was recently confirmed by Feiten and colleagues, who evaluated the effects of a very-low-protein diet supplemented with ketoacids in comparison to a conventional low-protein diet on nutritional and metabolic parameters in 24 CKD patients with advanced CKD. The authors showed that after 4 months of follow-up, nutritional status was adequately maintained with both diet regimens.[52] While the clinical efficacy and cost of such interventions have been questioned,[53,54] such interventions could not be easily applied to the majority of patients with CKD; thus, in the majority of patients who are not on a closely supervised diet, the development of progressive CKD is followed by a worsening in anorexia, decreased food intake, and possibly the development of PEW. In a follow-up report of the MDRD study participants, Menon and colleagues reported that compared to a low protein diet, assignment to a very-low-protein diet supplemented with ketoacids had no impact on delaying the progression to kidney failure, had no relationship with a composite outcome of kidney failure and death, and increased the risk of death in the long-term.[55]

Metabolic and Hormonal Derangements

Metabolic acidosis, which commonly accompanies progressive CKD, also promotes PEW by increasing protein catabolism.[56,57] Landmark studies by Mitch and colleagues showed that muscle proteolysis is stimulated by an ATP-dependent pathway involving ubiquitin and proteasomes during metabolic acidosis.[58,59] Ballmer and colleagues reported that a state of metabolic acidosis induced by high doses of ammonium chloride (NH_4Cl) (4.2 mmol/kg) lasting for 7 days significantly reduces albumin synthesis and induces negative nitrogen balance in otherwise healthy subjects.[60] Studies by Mochizuki showed that acidosis increases the degradation of branched-chain amino acids and branched-chain ketoacids in CKD patients.[61] Reaich and colleagues studied leucine kinetics and showed that the high rate of leucine oxidation in acidotic CKD patients, a potential catabolic factor, could be corrected after a 4-week treatment period with sodium bicarbonate and sodium chloride.[62] In 134 adult patients with stage 4 CKD and serum bicarbonate 16 to 20 mmol/L, de Brito-Ashurst and colleagues reported that supplementation with oral sodium bicarbonate for 2 years slows the rate of progression of renal failure to ESRD and improves nutritional status versus standard care.[63] A relevant issue that deserves mentioning is that in CKD patients' total bicarbonate concentrations generally decrease as kidney function worsens.[64] Because nPNA is actually estimated by measuring urinary urea nitrogen excretion in stable patients, considering the catabolic effects of metabolic acidosis,[25] the spontaneous DPI may actually be overestimated in patients with advanced CKD, when metabolic acidosis is most apparent. Once chronic dialysis is initiated, one would expect that the partial correction of serum bicarbonate concentrations due to dialysis would overcome, at least in part, the catabolic consequences of metabolic acidosis. Surprisingly, there is evidence that the catabolic effects associated with metabolic acidosis are not totally negligible even after maintenance dialysis is initiated. Lofberg and colleagues found that the muscle intracellular valine concentration was negatively correlated with the level

of plasma bicarbonate concentrations in MHD patients and that higher muscle intracellular concentrations of valine, leucine, and isoleucine were observed after providing dialysis patients with supplemental sodium bicarbonate for 6 months.[65] Similarly, Pickering and colleagues showed that 4 weeks of increased bicarbonate in the dialysate (from 35 mmol/L to a 40 mmol/L lactate dialysate) resulted in significant increases in weight, body mass index, and plasma branched-chain amino acid concentrations, whereas muscle levels of ubiquitin mRNA decreased significantly.[66]

Several hormonal derangements including insulin resistance, increased glucagon concentrations, and secondary hyperparathyroidism are also implicated as factors in the development of PEW in CKD patients.[57] A postreceptor defect in insulin responsiveness of tissues, mostly involving phosphatidylinositol 3-kinase (PI 3-kinase), is the most likely cause of insulin resistance and associated glucose intolerance in CKD.[67–69] Because the anabolic effects of insulin are thought to be mediated by activation of PI 3-kinase, suppressed PI 3-kinase activity may lead to activation of the ubiquitin-proteasome pathway and muscle protein degradation.[68] Among ESRD patients, enhanced muscle protein breakdown has been observed in patients with type II DM compared to ESRD patients without DM.[14,70] In the absence of DM or severe obesity, insulin resistance is detectable in dialysis patients and is strongly associated with increased muscle protein breakdown, even after controlling for inflammation.[15]

It has also been suggested that hyperparathyroidism usually seen in CKD is, at least in part, responsible for this decreased tissue responsiveness to insulin via inhibition of insulin secretion by pancreatic β-cells.[71,72] Increased concentrations of parathyroid hormone have been implicated as a protein catabolic factor in CKD by enhancing amino acid release from muscle tissue.[73] Finally, there are several abnormalities in thyroid hormone profiles of CKD patients, characterized by low thyroxine and triiodothyronine concentrations.[74] These changes resemble the changes seen in prolonged malnutrition in other patient populations,[75] and it has been suggested that the thyroid hormone profile of malnutrition,[76] and possibly of progressive kidney disease, is a maladaptive response to decreased energy intake in an effort to preserve overall energy balance.

It has been suggested that abnormalities in the physiological axis of growth hormone and IGF-I are important factors in the development of PEW in MHD patients. Growth hormone is the major promoter of growth in children and exerts anabolic actions even in adults, such as enhancement of protein synthesis, reduced protein degradation, increased fat mobilization, and increased gluconeogenesis, with IGF-I being the major mediator of these actions.[77] Although several studies have demonstrated that plasma concentrations of growth hormone actually increase during the progression of kidney disease, probably due to reduced growth hormone clearance, more recent evidence suggests that CKD is associated with the development of resistance to growth hormone actions at cellular levels.[78] Several studies have shown that recombinant human growth hormone administered at pharmacological doses induced a net anabolic effect in MHD patients confirming the potential role of GH resistance in the development PEW in this patient population (see hereafter).[79]

Inflammation

Due to its high prevalence in ESRD patients, chronic inflammation is proposed as a potential catabolic factor that worsens the nutritional status of these patients. Figure 12-3 depicts the potential causes of inflammation in CKD patients. Inflammation, more correctly termed systemic inflammatory response syndrome (SIRS), is a complex combination of physiological, immunological, and metabolic effects occurring in response to a variety of stimulators resulting from tissue injury to disease processes. Certain cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) are the primary mediators of these effects, and the predominant metabolic effects of these cytokines are catabolic.[80] Therefore, it is important for the host to limit their biological activities by eliciting a strong antiinflammatory response. However, in conditions where the inflammatory response is ongoing and cannot be controlled effectively, such as in chronic diseases, adverse effects on the host may result. In these circumstances, there are repetitive stimuli for cytokine release with subsequent adverse effects to the host.[81]

When one considers the metabolic effects of chronic inflammation, the nutritional consequences are evident. Proinflammatory cytokines are thought to play integral roles in muscle catabolism in models of inflammatory diseases.[82–84] Studies have shown the involvement of the proinflammatory cytokine network in the signaling cascade of ubiquitin-proteasome proteolytic pathway with E3α-II playing an important role.[85] Accordingly, elevated levels of IL-6 are associated with increased muscle proteolysis, and the administration of IL-6 receptor antibody can block this effect.[86] In surgical patients with sepsis where abundant levels of proinflammatory cytokines are considered to be the hallmark of the disease, there is profoundly increased whole body protein catabolism.[87]

Anorexia or suppression of nutrient intake is another well-established metabolic effect of inflammation. Clearly, proinflammatory cytokines such as IL-1 and TNF-α are capable of this effect.[88] Animal studies suggest that the direct effects of these cytokines on the satiety center probably explain this finding. Prostaglandins may be involved in this chronic process because prophylactic use of antiinflammatory agents blunts the anorectic effects of cytokines.[89] Furthermore, animal studies have also shown an increased skeletal muscle protein breakdown with TNF-α (with or without IL-1) administration.[88]

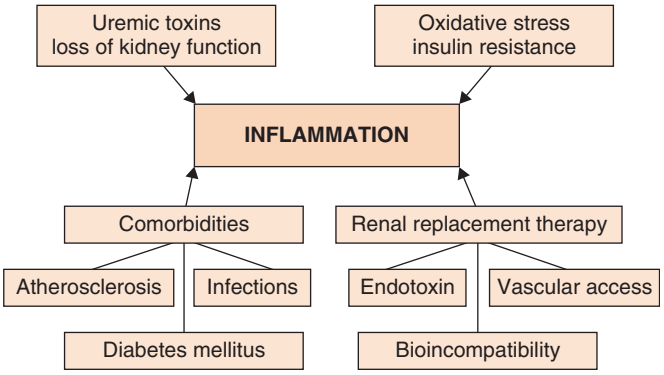


FIGURE 12-3 A number of modifiable and nonmodifiable factors lead to the chronic inflammatory state of advanced kidney disease.

A cross-sectional study by Kalantar-Zadeh showed that the extent of anorexia is closely and directly related to the level of plasma proinflammatory cytokine concentrations in MHD patients.[90] It should be noted that the combined presence of decreased nutrient intake at the time of increased protein breakdown during activated SIRS worsens the overall nitrogen balance, predisposing the patients to accelerated loss of skeletal muscle mass and overall poor nutritional state, which is a common scenario in CKD patients.

Several other indirect effects of chronic inflammation can also predispose CKD patients to hypercatabolism.[91] Chronic inflammation induces a decrease in voluntary activity, and the disease initiating the inflammation may require bedrest. Prolonged decrease in muscular activity is associated with muscle weakness, muscular atrophy, and negative nitrogen balance, which all lead to loss of lean body mass (LBM). Finally, there are certain hormonal derangements observed during chronic inflammation. These include disruption of the growth hormone and IGF-1 axis, leading to decreased anabolism and increased leptin concentrations, which may induce anorexia due its central effects.[92]

Dialytic Factors

The "safe level" of suggested protein and energy intake for normal individuals does not necessarily apply to dialysis-dependent patients, who may require higher levels due to concurrent abnormalities.[93] Numerous studies evaluating the actual protein requirements of dialysis patients suggest a minimum of 1.2 g/kg/d as a safe level of DPI for MHD and PD patients, based on several metabolic balance studies.[94] Obviously, despite the dialysis technology in use, there are a number of identifiable factors that justify the recommendations for increased requirement of protein intake in dialysis patients.

Catabolic Effects of the Hemodialysis Procedure

An additional cause of increased metabolic and nutritional stress in ESRD is the dialytic therapy. Earlier nitrogen balance studies by Borah and colleagues and Lim and colleagues suggested that the nitrogen appearance was higher on dialysis days even at high protein intake levels.[93,95] Subsequent studies unequivocally confirmed that the catabolic effects of hemodialysis, especially on the protein homeostasis, are profound, affecting both whole-body and skeletal muscle protein homeostasis. All of these studies consistently showed a decrease in protein synthesis at the whole-body level, whereas one specific study showed an additional increase in whole-body protein breakdown. In addition, two separate studies showed a significant increase in net skeletal muscle protein breakdown; in one study, these undesirable effects persisted for at least 2 hours following the completion of hemodialysis (Figure 12-4).[96–98]

Although not fully elucidated, the catabolic nature of dialysis is thought to be related to two concurrent issues: losses of amino acids via the dialysate and activation of inflammatory cascade. It has been clearly established that there are inevitable losses of amino acids into the dialysate during hemodialysis, which can be compensated by intradialytic nutritional supplementation.[99,100] While this is an important cause of hemodialysis related catabolism, the extent

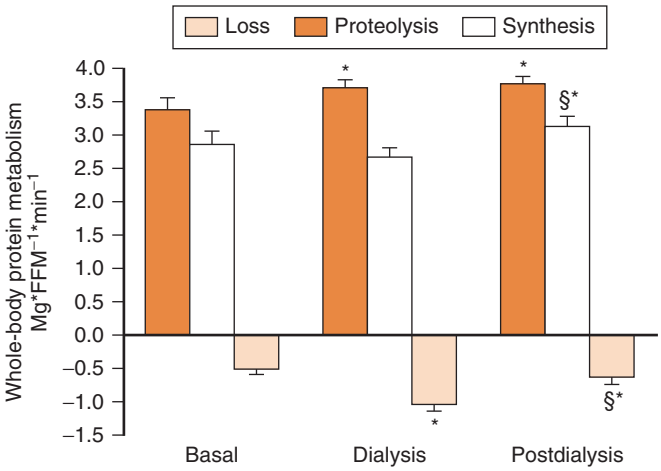


FIGURE 12-4 Metabolic effects of hemodialysis. Values reported are means ± SEM for each period. FFM, fat-free mass. * Significant difference from the basal period ($P < 0.05$); § Significant difference between the dialysis and postdialysis periods ($P < 0.05$). (Reprinted with permission from the American Physiological Society.)

of net negative nitrogen balance during HD is above and beyond of what can be accounted by nutrient losses alone.[96] Consistent with this is the observation of ongoing catabolism when infusion of intradialytic parenteral nutrition is turned off.[101] Several studies have shown that the hemodialysis procedure is associated with the activation of inflammatory cascade as evidenced by increases in CRP, IL-6, and fibrinogen fractional synthetic rate (Figure 12-5).[102] The activation of the inflammatory cascade has been attributed to exposure of blood to dialysis membranes and back-leakage of lipopolysaccharide through the dialysis membranes due to the use of less-than-sterile dialysate. In support of the latter, it has been shown that use of ultrapure, endotoxin-free dialysate resulted in reduced blood concentrations of proinflammatory cytokines.[103,104]

Dialysis Dose

An important and readily treatable cause of PEW in MHD patients is underdialysis, which can lead to at least anorexia and decreased taste acuity. The results of the National Cooperative Dialysis Study showed an association between lower

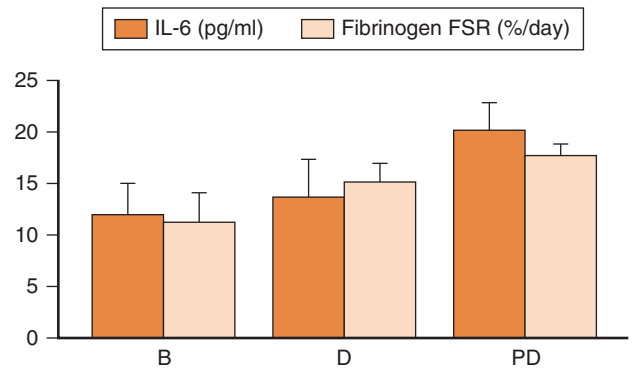


FIGURE 12-5 Interleukin-6 (IL-6) and fibrinogen fractional synthetic rate (FSR) assessed immediately before (B), during (D), and 2 hours post- (PD) hemodialysis. (Modified from K. Caglar, Y. Peng, L.B. Pupim, et al., Inflammatory signals associated with hemodialysis, Kidney Int. 62 [2002] 1408-1416, with permission.)

dietary protein intake and higher time-averaged urea concentrations, suggesting a relationship between underdialysis and anorexia.[105] Similarly, Lindsay and colleagues suggested that PNA (PCR) is dependent on the type and the dose of dialysis.[106] Bergstrom and Lindhom have also reported a significant linear relationship between Kt/V and PNA, all suggesting that anorexia is related to underdialysis.[107] However, both Kt/V and PNA are calculated from similar measures; therefore, whether there is a mathematical link between the two and whether decreased PNA would really reflect the nutritional status of these patients is still a subject of debate. In this respect, in a large cross-sectional study by Owen and colleagues, no statistically significant relationship between serum albumin and dose of dialysis was seen.[108] Furthermore, the HEMO study did not show any difference in serum albumin concentrations between the standard dose and higher dose treatment arms. Nevertheless, it is reasonable to assume that decreasing clearance of uremic toxins is associated with progressive anorexia at all stages of kidney failure.

Factors More Exclusively Related to Peritoneal Dialysis

Observations similar to the ones described previously for hemodialysis have been made for PD patients. However, PD patients require a lower dialysis dose as compared to MHD patients to achieve a given DPI.[107,109] It has been suggested that this might be due to a better removal of middle molecules by the peritoneal membrane, compared to the hemodialysis membrane, since these molecules are thought to be anorexigenic. Higher incidence of PEW has been reported in patients who are treated with continuous ambulatory peritoneal dialysis (CAPD) for longer than 3 months compared to patients who were treated for less than 3 months, suggesting that as residual kidney function decreases (a major contributor to total clearance in PD patients) indices of PEW become more evident.[110] Keshaviah and colleagues have also suggested that as residual kidney function declines in CAPD patients, PNA also decreases.[111] Teehan and colleagues and Lameire and colleagues reported higher survival rates and better nutritional markers with higher Kt/V.[112,113] Losses of proteins and amino acids into the dialysate fluid have long been identified as catabolic factors in PD patients. Several studies have reported a loss of 5.5 to 11.8 grams of proteins into the dialysate daily.[114] A large amount of these losses consist of albumin along with immunoglobulins and amino acids. Free amino acid losses have been estimated to be in the range of 1.7 to 3.4 grams per day according to different studies.[115] Most importantly, during episodes of peritonitis, these losses of proteins and amino acids increase substantially.[114] The generally lower serum albumin concentrations and several abnormalities in plasma amino acid profiles seen in PD patients are presumed to be results of these inevitable losses.

The amount of energy intake, at least indirectly, is relatively higher in PD patients, due to the absorption of glucose from the dialysate fluid. This absorption usually provides energy in the range of 5 to 20 kcal/kg/day in many patients, and it is a possible explanation for the relatively lower resting energy expenditure levels observed in this patient population.[116] Unfortunately, this absorption of glucose may also predispose these patients to further anorexia due to its satiety effect, in addition to the feeling of fullness related to the fluid in the peritoneal cavity. The presence of protein depletion in these patients, in spite of this increased energy consumption, is probably related to their inadequate intake of dietary protein because protein intake affects nitrogen balance more profoundly than the overall energy intake.[117] PD biocompatibility, which is the ability of a solution to allow adequate long-term dialysis without a clinically significant undesirable host response, systemically and locally (intraperitoneal) is tempered by continuous exposure to solutions with high concentrations of glucose, glucose degradation products, lactate, low pH, and high osmolality. All of these factors may change the structural and the function of the peritoneal membrane in the long-term. Use of a high concentration of bicarbonate as the solution buffer instead of lactate, or a physiological concentration of bicarbonate together with a markedly reduced concentration of lactate provides a means to deliver glucose-based solutions at a physiological pH.[118,119] Such solutions have a composition that is closer to that of the interstitial fluid and may therefore be more biocompatible with respect to peritoneal cells while at the same time providing equivalent or better correction of acidosis. Furthermore, the dual-chambered bag used to deliver these solutions has been designed to minimize the formation of glucose degradation products during heat sterilization. One compartment contains electrolytes at a high pH, whereas the other contains a high concentration of glucose at a low pH. Although these new PD solutions have not been associated with better nutritional outcomes, studies have suggested potential favorable effects on nutritionally-related conditions, such as metabolic acidosis.[120,121]

Medical Problems Inherent to Maintenance Dialysis

In addition to the previously mentioned factors, placement of permanent or temporary vascular accesses in chronic HD patients and the use of the peritoneal cavity in PD patients induce additional medical problems and hospitalizations due to infections and access revisions. Increased frequency of hospitalizations may adversely affect the nutritional status of maintenance dialysis patients.[122] The actual daily protein intake of chronic HD patients admitted to a regular ward is at very low levels (0.55 g/kg/d $\pm$ 0.33 g/kg/d), and simultaneous calculations of PNA by urea kinetics reveal a negative nitrogen balance in 80% of hospitalized patients.[26] Along with decreased PNA, serum albumin concentrations also decrease significantly with hospitalizations. Therefore, frequent hospital admissions may also be an insidious and important cause of PEW in chronic dialysis patients.

Factors Related to Kidney Transplantation

Although kidney transplantation probably offers the best nutritional rehabilitation for CKD patients at present, it is still associated with some degree of nutritional derangements, in spite of substantial reversal of the uremic state. The causes are multifactorial but can be divided into early and late phases. During the initial 6 weeks after the surgery, there is increased nutritional requirement due to the surgical metabolic stress itself and to the high doses of immunosuppressive medications, especially corticosteroids. Acute rejection and infection may also occur in the early phase and

may contribute to nutritional deficit. It is well-known that corticosteroids are associated with increased hepatic gluconeogenesis with elevated protein catabolism and decreasing visceral protein concentrations.[123–125] Studies by Miller and colleagues and Horber and colleagues have identified corticosteroid-associated abnormalities in anthropometrics and abnormalities in skeletal muscle ultrastructure in kidney transplant patients.[126,127] Hoy and colleagues also reported that increases in corticosteroid dosage further increased PNA.[128]

The late phase (after 6 weeks) is still marked by the deleterious effects of corticosteroids use, despite their adjusted doses. The nutritional problems commonly encountered during this phase are protein hypercatabolism, obesity, insulin resistance, and dyslipidemia. Studies have shown weight gain in a large number of transplant patients, mainly due to increased body fat,[129] which can be partially explained by the chronic use of immunosuppressive agents and liberalized diets. Nonetheless, serum albumin concentrations may still be low after 1 year following a kidney transplant, accompanied by increased concentrations of plasma and muscle amino acids.[130] A study by El Haggan and colleagues showed significant decreases in serum albumin, serum transferrin, and retinol-binding protein in 44 patients during the first year posttransplant.[131]

Another issue related to kidney transplant patients is the use of low-protein diets to alter the course of rejection. Although several uncontrolled and short-term studies suggested some preliminary immunological benefit on rejection, in a relatively well-designed study, significant decreases in almost all serum proteins, including serum total protein, albumin, prealbumin, and transferrin were observed with a diet consisting of 0.5 g/kg/day (low-protein) in kidney transplant patients with chronic rejection, whereas no significant changes occurred in GFR.[132] More recently, Bernardi and colleagues showed that a moderate protein intake of 0.8 g/kg/day along with sodium restriction, in attempts to avoid kidney hyperfiltration, stabilized long-term kidney function and maintained adequate nutritional status.[133] The results of another small-scale study actually suggested beneficial effects of a high protein diet with regard to side effects of corticosteroids.[134] Whether or not other factors, such as frequency of acute rejections, number of infectious complications, presence of chronic rejection, and other immunosuppressive agents play any role on the overall nutritional picture of the transplant patient remains to be determined.

PREVENTION AND TREATMENT OF PROTEIN-ENERGY WASTING IN CHRONIC KIDNEY DISEASE

Given the significance of the problem, and the complexity of the pathophysiological basis of PEW, it is evident that the prevention and treatment options of uremic malnutrition are both critical and complex. To date, there is not a single treatment approach that will alleviate the multiple adverse consequences of PEW in patients with CKD. In the subsequent section, we will provide an overview of established prevention and treatment options for PEW (general aspects) and specific therapeutic options for each group of patients (CKD, PD, MHD, and transplant), in addition to an overview of certain promising novel strategies.

General Aspects

Due to the number of factors affecting nutritional status in patients with CKD or ESRD, treatment should involve a comprehensive combination of maneuvers to diminish protein and energy depletion, in addition to therapies that will avoid further losses. Unfortunately, for some of the therapies currently in use, there are only empiric data showing clear benefits, if not data showing lack of benefits, although some are derived from secondary outcomes as part of large clinical trials. These include provision of adequate dialysis, treatment of metabolic acidosis, adjustments of dietary requirement and intake, prophylaxis and treatment of infections, and even factors that are not obviously linked to nutrition but affect the CKD or the ESRD patient in a way that may further affect nutrition, such as fluid overload. In general, increased dialysis dose is always recommended in patients with anorexia and insufficient dietary intake, unless there is no reason to believe the patient is underdialyzed and other factors for anorexia and low intakes have been identified. With regards to metabolic acidosis, even slight degrees should be corrected by oral supplementation with sodium bicarbonate or by altering dialysate buffer concentration. Exercise performance is another evolving therapeutic option that should be encouraged. Comorbid conditions such as DM and cardiovascular disease should be actively treated, and infectious diseases should be avoided and treated promptly. Likewise, signs of chronic inflammation should be elucidated, and all attempts should be made to eliminate the etiology of the inflammatory response.

Chronic Kidney Disease Patients not on Renal Replacement Therapy

A list of measures to prevent and to treat malnutrition at different stages of CKD is presented in Table 12-3. Several hormonal and metabolic derangements, such as insulin resistance and amino acid abnormalities, are currently not treatable in patients with progressive CKD. However, other factors that adversely affect the nutritional status of CKD patients, such as the extent of anorexia, may be altered. In light of the evidence suggesting that decreasing spontaneous dietary protein and energy intake is a prominent feature of decreasing kidney function and correlates with worsening in nutritional markers, it is obvious that any dietary intervention designed to limit dietary intake during the predialysis stage must be undertaken cautiously. Patients on restricted diets should be followed very closely for signs and symptoms of PEW, and necessary adjustments must be made if PEW is suspected. In particular, patients on dietary protein restriction should have provision for adequate energy intake.

For the majority of patients who are not on a closely monitored dietary protein restriction, evident signs of poor nutrition, such as spontaneous DPI less than 0.75 g/kg/d and energy intake less than 20 kcal/kg/d, serum albumin concentrations below 4.0 g/dl, and apparent decrements in other nutritional indices, such as transferrin, prealbumin, IGF-I, and LBM, may warrant initiation of hemodialysis or indication for kidney transplant.[53] Of note, patients initiating

TABLE 12-3 Therapeutic Strategies for Protein Energy Wasting in CKD Patients

CKD PATIENTS
Optimal dietary protein and energy intake (0.75-1.2 gm/kg/d of protein and 25-30 kcal/kg/d of energy)
Optimal timing for initiation of dialysis, before onset of indices of malnutrition
CDT PATIENTS
Appropriate amount of dietary protein intake (> 1.2 g/kg/d) along with nutritional counseling to encourage increased energy intake
Optimal dose of dialysis (Kt/V > 1.4 or URR > 65%)
Use of biocompatible dialysis membranes
Enteral or intradialytic parenteral nutritional supplements (hemodialysis) and amino acid dialysate (peritoneal dialysis) if oral intake is not sufficient (< 1.2 gm/kg/d of protein or < 25 kcal/kg/d of energy intake despite nutritional counseling)
Growth factors (experimental):
– Recombinant human growth hormone
– Recombinant human insulin like growth factor-1
Appetite stimulants (experimental)
Antiinflammatory interventions (experimental)
Other novel drugs
– Ghrelin
TRANSPLANT PATIENTS
Appropriate amount of dietary protein intake (0.75-1.2 gm/kg/d)
Avoidance of excessive use of immunosuppressives
Early reinitiation of dialytic therapy with proper steroid tapering in patients with chronic rejection

maintenance hemodialysis often already display signs of PEW.[135,136] The length of hospital stay, the mortality within the first 90 days after initiation of dialysis, and the long-term mortality were all better in patients who were initiated on dialysis early in their course of kidney failure compared to patients who were referred to dialysis rather late.[53,137] Other studies have indeed suggested better nutritional outcomes with early initiation of maintenance hemodialysis, although there are no randomized, controlled trials to prove this beneficial effect and that improvement in PEW might be the mediator of better death and hospitalization rates.[39,138] These comments should not be taken to imply that a high protein intake should be encouraged in patients with CKD; rather, we suggest that in cases where there is low protein and energy intake in patients on spontaneous (unrestricted) diets, DPI of less than 0.75 g/kg/d is an early warning sign for the development of PEW.

Chronic Dialysis Patients

Dose of Dialysis

In general, based on the previously-mentioned studies, it seems clear that an adequate dose of dialysis is required to prevent development of PEW. Studies by Lindsay and colleagues showed that PNA increased significantly in patients whose Kt/V values were increased, compared to no change in PNA in patients whose Kt/V values remained the same.[139] Similarly, Burrowes and colleagues and Acchiardo and colleagues observed significant increases in serum albumin concentrations in CHD patients after increasing dose of dialysis to adequate levels.[140] In a 4-year prospective cohort, Hakim and colleagues observed a decrease in mortality rates from 22.8% to 9.1% when dialysis dose was increased intentionally to 1.33 (measured by delivered Kt/V) in 130 CHD patients.[141] With regards to the adequacy of CAPD, similar conclusions can be derived from several retrospective studies that show significant correlations between dialysis dose and nutritional parameters.[142] A large-scale multicenter prospective study suggested a positive relationship between adequacy of dialysis and nutritional status in CAPD patients.[143,144] Therefore, there is evidence that increased dose of dialysis is beneficial or that, at least, we should attempt to maintain adequate dose of dialysis, as recommended by the K/DOQI guidelines (minimum spKt/V of 1.2 or URR of 65%), to avoid PEW. One must, however, consider the results from the HEMO Study and from the Adequacy of PD in Mexico study, which did not necessarily support increased dose of dialysis for better outcomes, including nutritional ones. Specifically, results from the HEMO study showed no difference in outcomes, including a decline in serum albumin, when comparing high hemodialysis dose (achieved single pool Kt/V (spKt/V) of 1.71 ± 0.11) versus low hemodialysis dose (achieved spKt/V of 1.32 ± 0.09).[145] Among many methodological points that have been discussed, it is noteworthy that both high and low HEMO study groups received, on average, a spKt/V above the K/DOQI recommendations, which might have contributed to the lack of differences reported. Although no definitive conclusion has been achieved as to whether increasing dose of dialysis further than K/DOQI guidelines will ameliorate outcomes, including nutritional status, we believe that these results give us no reason to aim for a dialysis dose lower than the K/DOQI recommended spKt/V greater than or equal to 1.2 (URR $\geq$ 65%).[146]

The ADEMEX trial was also a randomized trial that tested the hypothesis that a peritoneal Kt/V of 1.7 would give equivalent mortality outcomes to a peritoneal Kt/V of 2.1.[147] The K/DOQI guidelines recommend a Kt/V (kidney plus peritoneal) of 2 for all CAPD patients. The results from the ADEMEX study showed that Kt/V values above 1.7 provided no survival advantage and no differences in the changes in serum albumin, serum prealbumin, and serum transferrin, although they observed higher serum albumin concentrations in the high dose group, which was attributable to the slightly higher baseline value for this group. Like the HEMO study, ADEMEX had some methodological limitations, including the mix of incident and prevalent patients. Therefore, caution should be taken in presuming that all PD patients can safely be prescribed a peritoneal Kt/V of 1.7.[148] Although the specific level of optimal dose of dialysis, after which no further improvement in nutritional status is observed, has not been conclusively established, these findings should be rather reassuring to the nephrology community in that the K/DOQI targets might be sufficient, as highlighted by Schulman and by Prichard,[148,149] at least for mortality and nutritional outcomes.

Dialysis Membrane

The use of bioincompatible membranes has become very sporadic in many countries over the last decade. Nonetheless, because these membranes are still in use in some centers, we must comment on their catabolic and anorectic effects.[139,150] In a study comparing nutritional outcomes in patients dialyzed to biocompatible versus bioincompatible membranes,

Parker and colleagues showed that the biocompatible group significantly increased dry body weight, whereas no change in weight was observed in the bioincompatible group. In addition, the biocompatible group had an earlier and more marked increase in serum albumin concentrations, and consistently higher IGF-1 values.[151] Consistently, reports from the United States Renal Data System (USRDS) have suggested that use of bioincompatible membranes is associated with increased risk of death in comparison to the use of biocompatible membranes.[152] Whether altered nutritional status plays a role in this process is not clear. With all that said, it seems as though the nephrology community has decided to abolish the use of bioincompatible membranes, whatever the primary motivation is. Therefore, this issue can be considered as of historical significance.

Nutritional Supplementation

Oral Nutritional Supplementation

When the general measures fail to prevent development of PEW, nutritional supplementation should be considered. The effectiveness of oral nutritional supplementation has not been clear-cut in patients with ESRD. Until recently, the results have been mixed, and most available studies are hampered by design and power issues. Nevertheless, several more recent reports provide intriguing data on the effectiveness of oral nutritional supplementation in patients with ESRD, especially when provided intradialytically. In a detailed metabolic study, Veeneman and colleagues[97] reported the effects of feeding during hemodialysis on whole-body protein balance using stable isotope tracer methodology. The feeding was in the form of yogurt, cream, and protein-enriched milk powder, given as six equal portions during the hemodialysis procedure and on a nondialysis day. Their results showed that consumption of a protein- and energy-enriched meal during hemodialysis resulted in a positive protein balance to the same extent as on a nondialysis day. Pupim and colleagues[153] examined the efficacy of intradialytic oral nutritional (IDON) supplementation in comparison to no supplementation or intradialytic parenteral nutritional (IDPN) supplementation in eight MHD patients with signs of PEW. Both IDPN and IDON supplementation resulted in highly positive whole-body net balance, compared to neutral balance in the control session when no supplementation was provided. Similarly, skeletal muscle protein homeostasis during hemodialysis also improved with both IDPN and IDON compared to the unsupplemented group (Figure 12-6). Although the anabolic effects of parenteral supplementation dissipated in the postdialytic period, oral supplementation led to sustained anabolic effects.

The studies by Veeneman and Pupim indicate that oral feeding in patients on MHD results in acute improvements in protein balance. However, these studies are not designed to establish whether the apparent short-term benefits of oral nutritional supplementation will translate into long-term improvements in the overall nutritional status of the MHD patient with PEW. Several studies provide stimulating data regarding beneficial effects of prolonged oral nutritional supplementation in maintenance dialysis patients. Caglar and colleagues reported that intradialytic oral nutritional

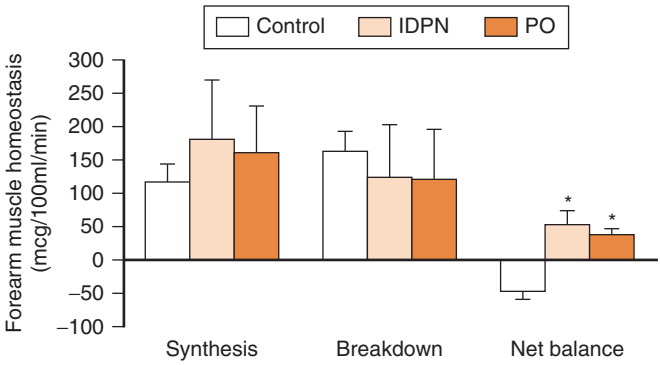


FIGURE 12-6 Forearm muscle protein homeostasis dynamic components during HD, comparing Control, IDPN, and PO in eight CHD patients with deranged nutritional status (see text). Skeletal muscle protein homeostasis during HD improved with both IDPN and PO versus control ($P = 0.005$ and 0.009 for IDPN versus control and PO versus control, respectively). PO resulted in persistent anabolic benefits in the post-HD phase for muscle protein metabolism, when anabolic benefits of IDPN dissipated (data not shown in figure). Units are mcg/100ml/min. *denotes $P < 0.05$ versus Control. (Adapted from L.B. Pupim, K.M. Majchrzak, P.J. Flakoll, T.A. Ikizler, Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status, J. Am. Soc. Nephrol. 17 [2006] 3149-3157, with permission.)

supplementation improved several nutritional parameters (including serum albumin and serum prealbumin concentrations and SGA) in a large group of MHD patients with PEW.[154] A significant aspect of this study was that nutritional supplementation was given during HD, which not only improved compliance but also provided supplements at a time when catabolism is at its highest level in these patients.[154] Kalantar-Zadeh[155] reported in a controlled design study that in hypoalbuminemic MHD patients, a short-term (4 weeks) in-center intradialytic oral nutritional intervention was associated with a significant increase in serum albumin level. The supplementation was found to be practical, convenient, and well-tolerated.

Daily (Nondialytic) Oral Nutritional Supplementation

While provision of nutrients during hemodialysis is an attractive approach, primarily due to the magnitude of the catabolic processes during dialysis, intradialytic oral nutrition by itself may be inadequate to achieve optimal dietary intake in certain subgroups of maintenance dialysis patients. For these patients, additional forms of supplementation such as enteral nutrition (including oral protein, amino acid tablets and energy supplementation, nasogastric tubes, and percutaneous endoscopic gastroscopy or jejunostomy tubes) can be considered.[156] Eustace and colleagues reported that oral amino acid supplements, administered three times a day over 3 months, significantly improved serum albumin concentration in MHD patients in a prospective, randomized, placebo-controlled pilot study.[157] Of note, subjects in the very low albumin strata (<3.5 g/dl) improved more than those in the low albumin strata (3.5 to 3.8 g/dl, $P < 0.01$). Improvements were also seen in hand-grip strength and SF-12 mental health score. These effects were more pronounced in the MHD patients than in peritoneal dialysis patients. In a metaanalysis, Stratton and colleagues performed a systematic review aimed at determining the

potential benefits of enteral multinutrient support (oral or tube) in MHD patients.[158] The outcome measures sought were clinical (quality of life, complications, and mortality), biochemical (albumin and electrolyte levels), and nutritional (dietary intake and anthropometry). The analysis included 18 studies (5 randomized controlled trials [RCTs], 13 non-RCTs) and suggested that enteral nutritional support increased total (energy and protein) intake and increased serum albumin concentration (on average by 0.23 g/dl), with no adverse effects on electrolyte status (serum phosphate and potassium). The authors also emphasized that the improvement in nutritional markers may well translate into improvement in clinical outcome, especially in patients with overt PEW.

Although provocative, the aforementioned studies can only be considered as preliminary. Despite a plethora of epidemiological data and a number of rather suboptimal designed interventional studies, it is important to recognize that causation cannot be inferred and that these findings warrant larger, randomized clinical trials. The results of a recent much larger magnitude and better designed study (French Intradialytic Nutrition Evaluation Study—FINEs) are now available to provide us such information, albeit with its coherent limitations (vide infra).[159]

Intradialytic Parenteral Nutrition

Although the gastrointestinal route is always preferred as the primary choice for nutritional supplementation, parenteral provision of nutrients, especially during the HD procedure (IDPN), has been shown to be a safe and convenient approach for ones who can not tolerate oral or enteral administration of nutrients. Several studies, though not all, showed strong evidence for nutritional improvements with the use of IDPN in MHD patients with overt PEW. Many of these studies that focused on IDPN involved a limited sample size over a short period, which hindered the ability of these trials to properly address the objective; hence, the observed inconsistency of the results between these studies.[160,161] The high cost of IDPN therapy and the regulatory concerns remain the greatest barriers to performing adequately powered RCTs.[162] As a result, there have been regulatory and financial concerns in advocating for the use of this potentially beneficial treatment.

In order to explore the acute metabolic effects of IDPN, Pupim and colleagues performed a randomized crossover study, where CHD patients with PEW (defined by serum albumin < 4 g/dl, serum prealbumin < 30 mg/dl, cholesterol < 150 mg/dl and serum transferrin < 150 mg/dl for 3 consecutive months) were studied with and without IDPN (IDPN and control protocols).[163] The results showed that IDPN promoted a 96% increase in whole-body protein synthesis and a 50% decrease in whole-body proteolysis compared to the control protocol. In addition, IDPN provided significantly higher forearm muscle protein synthesis compared to control (260%). Although there were no differences in forearm muscle proteolysis between protocols, the net result was a change from negative (muscle loss) to positive (muscle accretion) balance during IDPN administration (see Figure 12-6). The clinical relevance of this gain can be appreciated when one calculates that during the 3½ hours when IDPN was being infused during hemodialysis, approximately 51.5 grams of whole-body protein were anabolized compared to an essentially catabolic process in the absence of IDPN. If the body's fat-free mass is 73% of water, then the observed changes account for an uptake of an additional 191 grams of fat-free mass gain due to the IDPN treatment. In a subsequent study, same group reported that IDPN administration improved the hepatic synthesis of albumin as a part of improvements in the whole-body protein homeostasis. This was evidenced by significant increases in the fractional synthetic rate of albumin above and beyond what is observed due to HD alone.[164]

These preliminary observations provide evidence to support the limited number of long-term clinical studies reporting beneficial effects of IDPN administration in ESRD patients. Cano and colleagues, in an RCT, reported improvements in multiple nutritional parameters with IDPN in a group of 26 MHD patients with PEW.[165] In a retrospective analysis of more than 1500 MHD patients treated with IDPN, Chertow and colleagues have reported a decreased risk of death with the use of IDPN, particularly in patients with serum albumin concentrations below 3.5 g/dl and serum creatinine concentrations below 8 mg/dl; these patients showed substantial improvements in the nutritional parameters following use of IDPN.[160] Over a 9-month period, Mortelmans and colleagues prospectively evaluated 26 chronic hemodialysis malnourished patients who failed to improve with diet counseling. They reported significant increases in body weight, fat mass, and triceps skin-fold.[161]

Similar studies using amino acid dialysate (AAD) as a nutritional intervention in PD patients with PEW have also provided conflicting results. It is also worth mentioning that patients on PD are prone to muscle wasting through different mechanisms and therefore the observations regarding the causes and treatment strategies of PEW in MHD patients cannot be readily extrapolated to PD patients. Although detailed metabolic studies examining the role of amino acid and protein losses on protein turnover have not been performed, two metabolic studies have indicated beneficial effects of amino acid supplementation through dialysate. On the other hand, a long-term clinical trial did not show a conclusive nutritional improvement through such a strategy in PD patients.[166–168] Jones and colleagues have reported benefit from AAD, with increases in serum transferrin and total protein concentrations and a tendency of plasma amino acid profiles towards normal levels with one or two exchanges of AAD.[167] Of interest, there were significant improvements in serum albumin and prealbumin concentrations in those who had serum albumin concentrations in the lowest tertile.[167] It should also be noted that an increase in blood urea nitrogen concentration associated with exacerbation of uremic symptoms, and metabolic acidosis, remains a complication of AAD.[169] There are also several reports indicating increased circulating AGE and proinflammatory cytokine concentrations following AAD administration.

Overall, the abovementioned data suggest that IDPN and AAD may be useful in the treatment of MHD patients with PEW, and they offer an alternative method of nutritional intervention in whom oral or enteral intake cannot be maintained. As is the case for oral nutritional

supplementation, these data can only be considered as preliminary and there is need for large scale, well-designed nutritional intervention studies of IDPN in chronic dialysis patients with overt PEW. The results of FINE study could shed some light into this controversy, albeit with inherent limitations. Cano and colleagues randomly assigned 186 MHD patients with PEW to receive IDPN (for 1 year) and standard oral supplements providing 500 kcal/day and 25 g/day protein, or oral supplements alone.[159] The nutritional supplement goal was to bring patients' intakes up to the recommended amounts of 30 to 35 kcal/kg/day and 1.2 g/kg/day, respectively. The primary outcome, 2-year mortality, was similar in the two groups (39% in the control group and 43% in the IDPN group), suggesting that oral nutritional supplementation is equally effective as IDPN when oral intake is possible. Increases in prealbumin were associated with decreases in 2-year mortality and hospitalization rate, providing the first prospective evidence of a link between response to nutritional therapy and improved outcomes.

Several aspects of FINE study deserve attention. First, as the investigators point out, the route of administration of nutritional supplementation (i.e., oral or combined oral and parenteral) does not have any significant effect on survival in MHD patients with PEW, assuming that equal and adequate amounts of protein and calories are provided. Similarly, the route of administration does not influence the improvements in most nutritional markers that are observed following supplementation. These findings are not unexpected; several reports have shown that intradialytic oral and parenteral nutritional supplementation improve whole body and skeletal muscle protein homeostasis to a comparable extent in the short term (see Figure 12-6).[153] Second, despite the lack of an appropriate control group, the results of the FINE study imply that nutritional supplementation does indeed improve nutritional markers in CHD patients with PEW if the targets for dietary protein and energy intake recommended by the K/DOQI guidelines (>1.2 g/kg/day and >30 kcal/kg/day, respectively) are achieved (Figure 12-7).[31] It is of note that the improvement in serum albumin reported by Cano and colleagues (~2 g/L) is highly consistent with that described in the majority of other published studies reporting the effectiveness of nutritional interventions.[158] Third, the results imply that nutritional interventions in general improve survival in MHD patients. This conclusion should, however, be applied with caution because the study did not include a no-intervention arm. Although this is a critical limitation of the study, the authors appropriately note that it would have been unethical to withhold nutritional therapy. One can, however, compare the overall 2-year mortality rate in the study (42%) with the published mortality rate obtained from European registry data, adjusted for at least one of the FINE study inclusion criteria (a serum albumin <35 g/L; 49%). This comparison indicates an approximately 15% improvement in overall mortality with nutritional intervention, an impact on survival that is unmatched by any other proposed therapy for high-risk CHD patients to date. Finally, the results indicate that simple nutritional markers, such as serum prealbumin, can be used as surrogate markers not only of nutritional status but also possibly of hospitalization and survival.

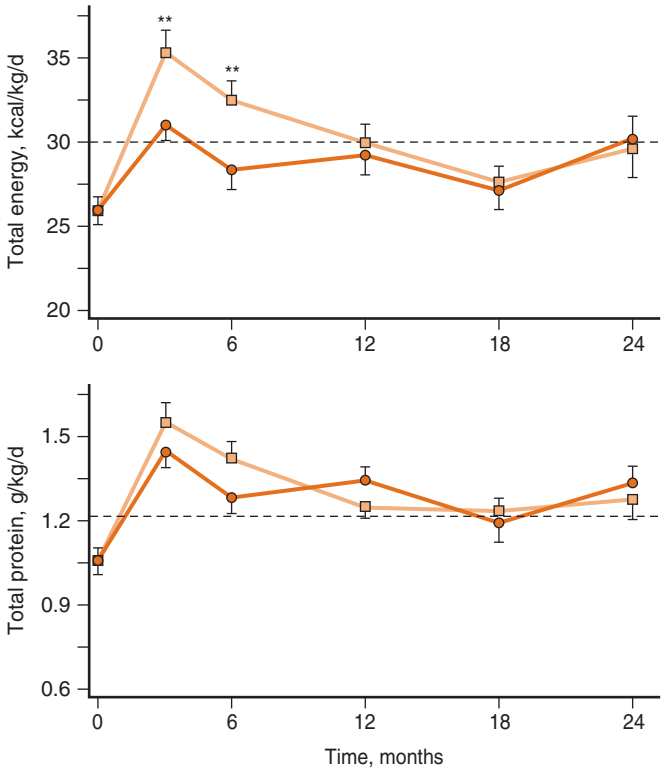


FIGURE 12-7 Changes in total energy and protein intakes during the 2-yr follow-up in control (black line) and IDPN (gray line) groups (means ± SEM) in the FINE study participants. While there were between-group differences in energy intake at months 3 and 6 ($P < 0.01$), both groups achieved the minimum K/DOQI recommended thresholds for protein and energy intake in maintenance hemodialysis patients (red dotted lines). In both groups, nutritional support induced comparable increases in serum albumin at months 3, 6, 12, and 18 ($P < 0.01$) and in serum prealbumin at months 3 to 24 ($P < 0.02$). (Adapted N.J. Cano, D. Fouque, H. Roth, et al., Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study, J. Am. Soc. Nephrol. 18 [2007] 2583-2591, with permission.)

Anabolic Agents

Patients on maintenance dialysis have low circulating levels of certain anabolic hormones (testosterone), resistance to other anabolic hormones (growth hormone [GH] and IGF-I) and increased levels of some catabolic hormones (cortisol). These hormonal derangements, individually or collectively, contribute to the development or worsening of PEW. It is therefore reasonable to speculate that pharmacological doses of anabolic hormones could be of potential value in the treatment of PEW of maintenance dialysis patients.

Growth Hormone

Abnormalities in the physiological axis of GH and IGF-I have been long-established.[170] GH is the major promoter of growth in children and exerts anabolic actions even in adults, such as enhancement of protein synthesis, reduced protein degradation, increased fat mobilization, and increased gluconeogenesis, with IGF-1 being the major mediator of these actions.[171] A few controlled studies were performed in a small number of patients for short periods, showing the consistent results on reducing protein catabolism, increasing

LBM and visceral protein concentrations (serum albumin and transferrin).[172–175] Most recently, a phase II randomized, double-blind, placebo-controlled, 26-week proof-of-concept clinical trial in 139 adult chronic HD patients showed that GH led to statistically significant gains in LBM as compared to placebo.[79] Statistically significant beneficial changes in other cardiovascular biomarkers of mortality (transferrin, high density lipoprotein, homocysteine) and quality of life were observed. There was also a trend ($p = 0.06$) toward increased levels of serum albumin as compared to placebo. Although this promising phase II trial was followed by a large-scale, 2-year clinical trial (OPPORTUNITY study) testing whether GH will produce improvements in mortality, it was prematurely terminated due to slow recruitment.[176]

Anabolic Steroids

As many as 50% to 70% of men with stage 5 CKD have been reported to be hypogonadal on the basis of low concentrations of total and free testosterone.[177] These disorders often worsen even after initiation of maintenance dialysis treatment.[178] Testosterone abnormalities have recently been linked to disorders in bone composition[179] and endothelial dysfunction in MHD patients.[180] A prospective observational study showed the significant inverse correlation between testosterone levels and all-cause and cardiovascular disease–related mortality in 126 MHD patients during a mean 41 follow-up months.[181] Strong inverse independent correlations were also observed between testosterone and various inflammatory markers. These observational data encourage further research into the role of testosterone as a modifiable risk factor in CKD and create a rationale for randomized controlled trials with testosterone supplementation in this patient group. Despite positive results of increased muscle mass and strength in several other clinical populations, such as elderly patients, patients with chronic obstructive pulmonary disease, and patients with HIV wasting, there has not been a clinic trial showing the effect of testosterone on CKD patients.

Nandrolone Decanoate

Nandrolone decanoate (ND), a non-17α-alkylated modified androgen analogue of testosterone, appears to be effective in increasing LBM and muscle strength in dialysis patients. In an RCT, Johansen and colleagues assessed body composition, muscle strength, and physical functioning while administering 100 mg of ND intramuscularly weekly for 6 months in 79 MHD patients.[182] Compared to baseline, ND induced a 4.5 kg LBM gain and a fat loss of 2.4 kg along with significant improvements in quadriceps muscle cross-sectional area measured by MRI and physical functioning. A dose-finding study in 54 patients on HD or PD explored the efficacy and safety of low, medium, or high doses of ND (50, 100, or 200 mg/week for 24 weeks, respectively, in males and half the dose in females).[183] The results indicated that ND increased appendicular LBM in a dose-responsive manner. It was also noted that in the majority of patients ND did not increase fluid retention in excess of that associated with protein accretion and suggested dosing of ND up to 200 mg/week in males and 50 mg/week in females could be further investigated to improve body composition. On the other hand, there were notable side effects such that highest dose of ND (100 mg/week) was intolerable in females because of virilizing effects. Other potential side effects included voice change and hirsutism in women, abnormalities in prostatic markers in men, liver tests and lipid metabolism in both genders, all of which indicate that patients in future studies should be regularly followed.

Ghrelin

Ghrelin is a peptide that activates neurons of the arcuate nucleus of the hypothalamus, an area known to be important in the regulation of feeding. Ghrelin is also an endogenous ligand for the growth hormone secretagogue (GHS) receptor type 1a. Parenteral or oral administration of a ghrelin-mimetic GHS have been shown to restore levels of growth hormone and IGF-I in older persons to levels seen in young adults.[184] Ghrelin provides further benefit in muscle wasting conditions via its appetite stimulating (orexigenic) and anti-inflammatory effects.[184,185] An RCT by Nass and colleagues showed that a particular ghrelin mimetic given over 2 years had significant anabolic effects and age-associated changes in body composition with an excellent side-effect profile.[186]

These distinct properties along with promising data in otherwise elderly population make ghrelin and ghrelin analogues part of an attractive therapeutic strategies for the treatment of PEW in chronic disease states, such as CKD. Indeed, in an experimental study, administration of ghrelin and two synthetic ghrelin-receptor agonists (BIM-28125 and BIM-28131) increased food intake, attenuated muscle protein degradation, and decreased circulating inflammatory cytokines in nephrectomized animals.[187] Wynne and colleagues administered subcutaneous ghrelin and saline placebo in a randomized, double-blind, crossover protocol to nine PD patients with mild to moderate malnutrition. Administration of subcutaneous ghrelin significantly increased short-term food intake without any significant side effects.[188]

Antiinflammatory Interventions

There are only a limited number of studies evaluating the antiinflammatory interventions aimed at ameliorating the adverse effects of chronic inflammation on nutritional status, especially in ESRD patients (see Table 12-3). Pentoxifylline and resistance exercise are the only antiinflammatory interventions shown to have an effect on nutritional markers in ESRD patients. Biolo and colleagues investigated the ability of pentoxifylline, a drug known to block TNF-α release, to modulate whole-body protein kinetics in stages 4 to 5 CKD patients.[189] Intravenous infusion of pentoxifylline alone not only improved protein breakdown, but also augmented the anabolic effects of a balanced amino acid mixture administration. In addition, although pentoxifylline infusion did not significantly affect TNF-α levels, it decreased TNF-α-soluble receptors both in the postabsorptive state and during hyperaminoacidemia. Although not directly proposed as an antiinflammatory intervention, Castaneda and colleagues reported in a pilot study that 12 weeks of resistance exercise training resulted in simultaneous improvements in whole-body protein balance and inflammatory markers in stages 3 to 4 CKD patients.[190]

In addition to pentoxifylline and resistance exercise, a number of other antiinflammatory interventions that have been studied in other patient populations have been

proposed in ESRD patients as well. These include, but not limited to thalidomide, IL-1 receptor antagonist, TNF-α receptor blockers, fish oil, statins, angiotensin converting enyzme inhibitors, peroxisome proliferator activated receptor-gamma agonists and certain antioxidants.[191] A pilot study by Himmelfarb and colleagues indicated that combined administration of gamma tocopherol and docosahexaenoic acid over 3 months resulted in significant decreases in IL-6 and white blood cell count in 70 chronic HD patients.[192] Although preliminary, these results are encouraging and clearly indicate the need for further larger scale studies.

Appetite Stimulants

Because anorexia is sometimes not easily treatable by usual measures such as increased dialysis dose, the use of appetite stimulants is a promising and tempting component of a comprehensive therapy for PEW. Examples of pharmacological agents that may stimulate appetite include megestrol acetate, dronabinol, cyproheptadine, melatonin, and thalidomide. Most of these drugs have not been studied, at least systematically, in the CKD population. The most extensively studied drug is megestrol acetate, a steroid like progestogen used for the treatment of breast cancer, which caused increased appetite and weight gain as an unexpected side effect.[193] In elderly men, the orexigenic and weight gaining effects of megestrol acetate have been recently attributed to its anticytokine effects via reduced levels of IL-6 and TNF-α.[194] Interestingly, associated with the increased appetite, body weight, and quality of life, the weight gain was mainly due to increased fat but not LBM.[195] Moreover, megestrol acetate has been associated with important side effects that remain to be evaluated in detail including hypogonadism, impotence, and increased risk of thromboembolism. Therefore, although megestrol acetate has been shown to stimulate appetite[196,197] and induce small increases in serum albumin in pilot studies in dialysis patients,[198] large-scale prospective studies are needed to assess whether these drugs are of value as an adjunctive nutritional therapy in all stages of CKD.[196,199] To the best of our knowledge, no studies have been performed to study the appetite-stimulating and weight gain effects of dronabinol, cyproheptadine, melatonin, and thalidomide in CKD patients.

Combination Anabolic Interventions

A potential strategy to augment the anabolic effects of nutritional supplementation is concomitant exposure to resistance exercise around the time of administration of nutritional supplementation. Short-term studies in healthy subjects and MHD patients showed that postexercise net muscle protein accretion is increased with oral nutrition supplement when compared to exercise or oral supplement alone.[200,201] A metabolic study by Pupim and colleagues indicated an incremental beneficial effect of GH, IDPN, and exercise in MHD patients, at least in the acute setting.[202] Johansen and colleagues showed that exercise and ND induced an additive increase in muscle cross-sectional area, albeit to a small extent.[182] There are no long-term studies examining whether these acute changes would translate into long-term benefits in muscle mass and strength in maintenance dialysis patients.

Economic Implications of Nutritional Interventions

It is also important to assess the impact of nutritional supplements not only in terms of changes in nutritional parameters, but to extrapolate these observations to potential improvements in hospitalization, mortality, and cost-effectiveness. Lacson and colleagues showed that a hypothetical increase in serum albumin concentration in the order of 2 g/L in 50% of the United States' dialysis population would be associated with projections of approximately 1400 lives saved, approximately 6000 hospitalizations averted, and approximately $36 million in Medicare cost savings resulting from a reduction of approximately 20,000 hospital days over 1 year.[203] This is a reasonable estimation because 2 g/L increase in serum albumin is the average improvement reported in most nutritional intervention studies.[158]

Transplant Patients

As is the case with other aspects of nutrition in transplant patients, the prevention and the treatment of PEW has not been studied in detail. Similarly, the impact of obesity and strategies to prevent or treat it has not been examined in detail. However, one can propose that such interventions should include avoiding unnecessary or excessive use of catabolic agents, particularly in patients with frequent acute rejection episodes in their early transplant stages. For patients with chronic rejections, it is crucial not to delay the initiation of RRT and provision of an efficient tapering of corticosteroid dosages. It is a common experience that most transplant patients who are initiated on RRT are still on chronic corticosteroid therapy, which for most patients is unnecessary.

It is clear that much work is needed in this patient population with regard to nutrition. Therefore, studies that evaluate the importance of overnutrition and undernutrition in transplant patients with acute and chronic rejection should be encouraged. Finally, the importance and efficacy of GH in pediatric uremic and transplant patients have been highlighted by several studies.[204,205]

Dietary Supplements

The use of complementary and alternative medicine (CAM) is common in developed countries. Importantly, most individuals use CAM without counseling a healthcare provider. Given the limited premarket safety and efficacy testing and use of these supplements as mixtures, it is not unreasonable to expect that CAM usage is associated with nephrotoxicity. Of note, most of the side effects are described as case reports, which may be related to voluntary reporting.[206] In addition, reports of contamination of dietary supplements are common, although very few cases of CAM adulteration have resulted in renal injury.

Aristolochic acid is the most well-documented adulterant with renal injury.[207] The particular correlation between nephrotoxicity and CAM use was initially noted when nine Belgian women presented with rapidly progressing renal failure as a result of biopsy-proven tubulointerstitial

nephritis. Interestingly, all had consumed the same weight-loss supplement. Chromatographic analysis of the supplement revealed that the preparation had been adulterated with *Aristolochia*. Several additional case reports have demonstrated the nephrotoxic properties of aristolochic acid, leading to what is called "Chinese herb nephropathy" with extensive interstitial fibrosis with tubular atrophy and loss. There are also recent reports to indicate that aristolochic acid may also be associated with Balkan endemic nephropathy, although a definite association remains unproved. In addition, exposure to aristolochic acid increases the risk for urothelial malignancies. Most recently, serious illnesses and deaths of babies in China were linked to melamine-tainted powdered infant formula. Melamine contains several metabolites, such as ammeline, ammelide, and cyanuric acid, and has been used for the adulteration of foods or milk to increase their apparent protein content.[208] Other common contaminants, such as the heavy metals (e.g., arsenic, lead, mercury) and synthetic drugs (e.g., indomethacin, ibuprofen, phenylbutazone, mefenamic acid), may also have potential to induce acute or chronic renal injury.

Obesity in Chronic Kidney Disease and End-Stage Renal Disease

An equally important issue to consider in maintenance dialysis patients is the relevance of overweight and obesity. Obesity and overweight are established risk factors for developing CKD in healthy populations. In earlier CKD stages, obesity is a cardiovascular and metabolic risk factor comparable to that seen in the general population. In theory, decreased weight may have beneficial effects on the glomerular hemodynamics, although there are no prospective studies that examined the effects of intentional weight loss in CKD patients. In spite of the potential adverse consequences of obesity in earlier stages of kidney disease, there is now a plethora of epidemiological studies indicating that higher body mass index, regardless of its etiology (i.e., increased adiposity or LBM) is associated with significantly better survival in ESRD patients.[209] Although the exact mechanism(s) underlying this association have not been elucidated, it points to a potentially beneficial effect of increasing the protein and energy intakes to levels higher than those required to maintain a neutral nitrogen balance alone, if weight gain is one potential outcome of this intervention.[210]

ACKNOWLEDGMENTS

This work is supported in part by NIH Grant K24 DK62849 and R01 DK45604 from the National Institute of Diabetes, Digestive and Kidney Diseases and Clinical Translational Science Award 1UL-1RR024975 from the National Center for Research Resources. Lara B. Pupim is currently an employee of Bristol Myer Squibb and declares no conflict of interest with the content of this work.

A full list of references are available at www.expertconsult.com.

Chapter 13

INFLAMMATION IN CHRONIC KIDNEY DISEASE

Csaba P. Kovesdy, M.D. and Kamyar Kalantar-Zadeh, M.D., M.P.H., Ph.D.

Chronic kidney disease (CKD) affects about 20 million patients in the United States,[1] with approximately 450,000 patients of them having end-stage renal disease (ESRD) and requiring maintenance hemodialysis, and 150,000 having a kidney transplant.[1] These patients experience lower quality of life, greater morbidity, higher hospitalization rates, and increased mortality. In spite of improvements in dialytic therapies, dialysis patients continue to experience very high annual mortality rates of approximately 20%, with elevated incidence and prevalence of cardiovascular disease.[2] Clinical trials[3] have failed to show a survival advantage from higher dialysis dose or better dialyzer membrane quality in ESRD patients.[4,5] Interventions designed to improve traditional risk factors of cardiovascular disease such as hypertension, hypercholesterolemia, obesity, and hyperhomocysteinemia have failed to result in improved outcomes in ESRD patients.[6–10] The disappointing results of interventions with proven benefits in the general population have put the spotlight on novel, nontraditional mechanisms of cardiovascular disease and mortality including chronic inflammation and its related conditions in patients with CKD.

INFLAMMATION IN THE GENERAL POPULATION

Local or generalized inflammatory processes are inherent defense mechanisms in the human body. The acute phase response is a major pathophysiological phenomenon that accompanies inflammation. With this reaction, normal homeostatic mechanisms are replaced by new set points that presumably contribute to defensive or adaptive capabilities. C-reactive protein (CRP) is probably the best known inflammatory molecule in human biology. It was first described in the 1930s for its role in serological reactions to pneumococcal pneumonia.[11] CRP, a pentagon-shaped protein produced by the liver, binds to phosphocholine leading to recognition of foreign pathogens and phospholipid constituents of damaged cells.[12] The bound CRP not only activates complement, but also binds to phagocytic cells to initiate elimination of targeted cells by interaction with both humoral and cellular effector systems including inflammatory cytokines such an interleukin (IL)-1β and IL-6 (Figure 13-1).[12]

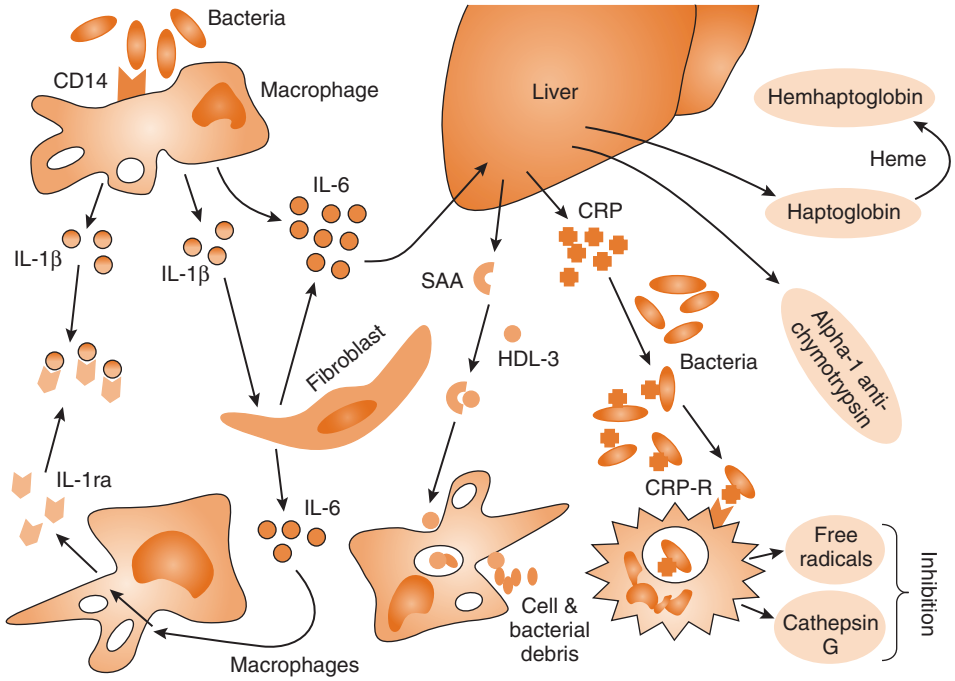


FIGURE 13-1 Role of inflammatory molecules in defense against bacterial infection.

The rapidity of the CRP response—in contrast to the slower adaptive immune response represented by antibody production—makes it one of the fastest soldiers of the "special force" of our immune system known as "acute phase response." Under such acute conditions, serum CRP level can surpass the 50 mg/L range but returns to normal (<0.5 mg/L or <0.05 mg/dl) once the infection subsides (Figure 13-2).[13] The problem arises, however, when these destined-to-be "acute" soldiers circulate chronically in our vessels.[14] The chronically elevated CRP levels, usually between 1 and 5 mg/L and sometimes even up to 50 mg/L, are associated with subsequent endothelial dysfunction and atherosclerotic cardiovascular disease.[15] To that end, it is not surprising to observe such an unacceptably high burden of atherosclerotic cardiovascular disease and death in CKD and dialysis patients in whom CRP levels are not infrequently found in ranges between 5 to 50 mg/L (see Figure 13-2). Hence, despite its name, the "acute" phase response can persist over months to years and, hence, it becomes "chronic inflammation".

CHRONIC INFLAMMATION IN CHRONIC KIDNEY DISEASE

Recurrent or chronic inflammatory processes are common in individuals with both nondialysis dependent (NDD) CKD and ESRD undergoing dialysis. This is due to various factors, including the uremic milieu, elevated levels of circulating proinflammatory cytokines, oxidative stress, carbonyl stress, protein-energy wasting, enhanced incidence of infections (especially dialysis access-related) and others (see Table 13-1). Although the definition of inflammation is unclear in this setting, CKD-associated chronic

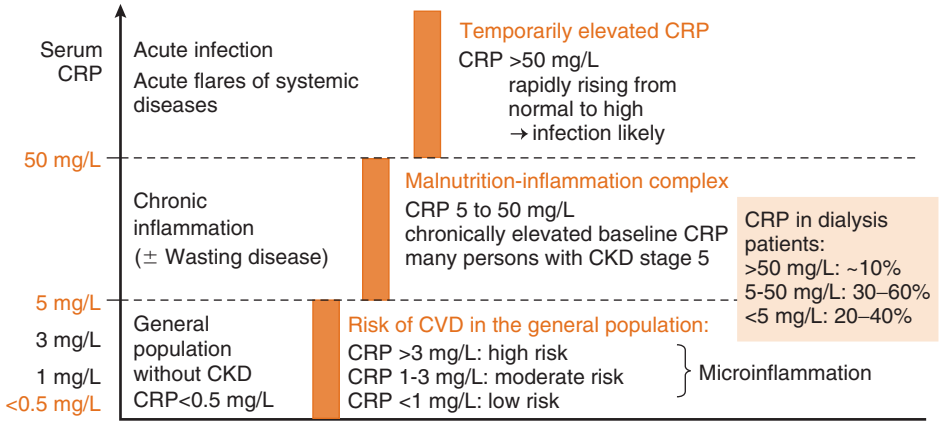


FIGURE 13-2 Classification of CRP ranges in the general population and in CKD patients.

TABLE 13-1 Potential Contributors of Inflammation in CKD

A. CAUSES OF INFLAMMATION IN CKD INDEPENDENT OF DIALYSIS TREATMENT/TECHNIQUE
1. Decreased clearance of proinflammatory cytokines
2. Volume overload
3. Oxidative stress
4. Carbonyl stress
5. Increased level of endotoxins
6. Decreased levels of antioxidants
7. Deteriorating protein-energy nutritional state and food intake
8. Increased susceptibility to infection in uremia
9. Genetic factors such as low production of antiinflammatory cytokines
10. Inflammatory diseases with kidney involvement (SLE, HIV, etc.)
11. Increased prevalence of other comorbid conditions
12. Remnant (failed) kidney transplant
B. ADDITIONAL CONTRIBUTING FACTORS RELATED TO DIALYSIS TREATMENT
I. HEMODIALYSIS:
1. Exposure to dialysis tubing
2. Dialysis membranes with decreased biocompatiblility (e.g., cuprophane)
3. Impurities in dialysis water and/or dialysate
4. Back-filtration or back-diffusion of contaminants
5. Foreign bodies, such as PTFE in current or remnant vascular access
6. Intravenous catheter
II. PERITONEAL DIALYSIS:
1. Episodes of overt or latent peritonitis
2. PD-catheter as a foreign body and its related infections
3. Constant exposure to PD solution

CKD, chronic kidney disease; *GFR*, glomerular filtration rate; *HIV*, human immunodeficiency virus; *PD*, peritoneal dialysis; *PTFE*, polytetrafluoroethylene; *SLE*, systemic lupus erythematosus.

inflammation, measured by CRP levels greater than 5 mg/L over at least 3 months, has been reported in 20% to 60% of North American and European dialysis patients, with a lower prevalence among dialysis patients in Asian countries.

CHRONIC KIDNEY DISEASE-SPECIFIC CAUSES OF INFLAMMATION

The exact causes of inflammation in CKD remain ill defined, but it is likely that a number of factors contribute to the initiation and maintenance of an inflammatory state, as listed in Table 13-1. These include intercurrent illnesses,[16–18] various comorbidities,[19–21] decreased glomerular filtration rate,[22] and various factors related to the dialysis procedure.[23–29]

Decreased Clearance of Proinflammatory Cytokines

Decreases in renal function may enhance overall inflammatory responses because of the lower renal clearance of factors that are directly or indirectly involved in inflammation. As an example, the serum half-lives of proinflammatory cytokines, tumor necrosis factor-alpha (TNF-α) and IL-1, are greater in animals without renal function than they are in animals with renal function.[30,31] In humans, declining renal function may also affect the levels of additional inflammatory molecules, because serum CRP, IL-6, and hyaluronan levels are inversely correlated with creatinine clearance.[32,33] In addition, among ESRD patients with residual renal function, higher serum CRP concentrations are observed among those with relatively less native kidney function.[22,34]

Volume Overload

Vascular congestion from fluid overload may result in altered permeability of the gastrointestinal tract, thereby leading to accumulation of endotoxins such as lipopolysaccharides and bacteria. These processes may in turn stimulate monocytes and the increased release of proinflammatory cytokines.[35,36] In a study of patients with decompensated congestive heart failure, successful diuretic therapy resulted in resolution of their edema and a significant decrease in blood endotoxin levels.[21] It is unclear to what extents the findings of these studies apply to patients with CKD, but the periodic and often marked volume expansion present in hemodialysis patients make this patient group especially prone to such a pathophysiological mechanism.

Oxidative and Carbonyl Stress

Increased production of cytokines induced by oxidative stress is also observed among patients with CKD and ESRD.[37] Oxidative stress, which occurs when there is an excessive free-radical production or low antioxidant level, is a possibly important condition for the development of endothelial dysfunction, inflammation, and atherogenesis.[37–39] Lower plasmalogen levels, which are indicators of such stress, have been reported in malnourished and inflamed patients with CKD.[40] With renal dysfunction, molecules that are not cytokines may also accumulate and provoke an inflammatory response. As an example, advanced glycosylated end products (AGE), which result from carbonyl stress, can clearly initiate inflammation in patients with CKD and especially in patients with ESRD.[41,42]

Decreased Antioxidant Levels

The oral intake or the level of some antioxidants is lower than normal in both CKD and ESRD patients.[43] An acute-phase response is also associated with decreased plasma levels of several antioxidants, such as serum vitamin C concentrations.[44] Low serum vitamin C levels are in turn associated with increased cardiovascular morbidity and mortality.[45]

Comorbid Conditions

The frequent occurrence of various comorbid illnesses in CKD patients promotes a hypercatabolic state and the development of inflammation.[46] Increased CRP levels have been associated with periodontal disease,[47] even in the absence of overt clinical illness.[48] Furthermore, an increased susceptibility to infections is typical in dialysis patients, partly due to uremia, old age, and other comorbid conditions.[49]

Other Factors

Systemic autoimmune diseases (which could have been the etiology of CKD), genetic factors, unrecognized persistent infections, and atherosclerosis may also underlie inflammation among patients with CKD or ESRD.[50–52]

END-STAGE RENAL DISEASE-SPECIFIC CONTRIBUTORS OF INFLAMMATION

Hemodialysis

In addition to the previously mentioned causes that may underlie and enhance ongoing inflammation in patients with CKD, the following conditions may cause or enhance inflammatory processes in patients undergoing maintenance hemodialysis:

1) Exposure to dialysis tubing and dialysis membranes, particularly less biocompatible membranes (e.g., cuprophane membranes).[27,53]
2) Poor quality of dialysis water and back-filtration or back-diffusion of contaminants, resulting in possible exposure to endotoxins. The use of ultrapure dialysate has been shown to result in improvement in nutritional status, a decrease in the concentration of inflammatory markers, and slower decline in residual kidney function.[54–56]
3) The presence of foreign bodies (such as polytetrafluoroethylene chronic access grafts) or intravenous catheters, which may harbor chronic or recurrent latent infections.[57] Insertion of dialysis catheters has resulted in an increase, and removal of catheters in a decrease in CRP levels in a small observational study of chronic hemodialysis patients.[58]

Peritoneal Dialysis

In addition to the previously mentioned mechanisms, factors unique to peritoneal dialysis (PD) patients may also result in enhancement of chronic inflammation:

1) Episodes of overt or latent peritonitis or PD catheter-related infections[59,60]
2) Constant exposure to PD solution, which may include bioincompatible substances or endotoxins[59,60]
3) Loss of residual renal function and volume overload[59]

Presence of a Failed Kidney Transplant

A chronic inflammatory state has been noted in patients who return to dialysis after failed kidney transplants and in whom the nonfunctioning allograft is retained. Symptoms and signs of inflammation may abate with the removal of the failed allograft.[61]

MARKERS OF INFLAMMATION IN CHRONIC KIDNEY DISEASE

The inflammatory reaction is a complex cascade of events that involves several mediators and affects multiple different cell types (see Figure 13-1). The presence of inflammation can be diagnosed by measuring one or more components involved in this process (Table 13-2). This can be done by assessing widely available (and relatively inexpensive) biomarkers such as serum albumin or the white blood cell

TABLE 13-2 Inflammatory Markers in Patients with CKD

CATEGORY	MARKER (AND COMMONLY USED ABBREVIATION)
Short pentraxins	C-reactive protein (CRP) Serum amyloid P (SAP)
Long pentraxins	Pentraxin-3 (PTX3) neuronal pentraxins
Proinflammatory cytokines	Interleukin-6 (IL-6) Interleukin-1 beta (IL-1β) Tumor necrosis factor alpha (TNF-α) Interleukin-8 (IL-8) Interleukin-18 (IL-18) Interleukin-12 (IL-12) Interferon gamma (IFNγ)
Antiinflammatory cytokines	Interleukin-10 (IL-10) IL-1 receptor antagonist (IL-1ra) Interleukin-4 (IL-4) Transforming growth factor-beta (TGF-β)
Adipokines and related compounds	Adiponectin Visfatin Resistin Leptin CD163
Adhesion molecules and endothelial markers	Intercellular adhesion molecule-1 (ICAM-1) Vascular cell adhesion molecule-1 (VCAM-1) E-selectin
Coagulation markers	Fibrinogen Tissue plasminogen activator (t-PA) Plasminogen activator inhibitor-1 [PAI-1]), von Willebrand factor (vWF) and factor VII Fibrin D-dimer
Inflammatory molecules with negative acute phase reaction	Albumin (negative) Transferrin or TIBC Iron Fetuin
Inflammatory lipoproteins	HDL inflammatory index (HII) Oxidized LDL (oxLDL)
Inflammatory enzymes	Myeloperoxidase (MPO) matrix metalloproteinase (MMP-9)
Proinflammatory transcription factors	Activator protein-1 (AP-1) Nuclear factor-κB (NF-κB)
Other inflammatory markers	Serum ferritin Serum amyloid A (SAA) Neopterin (monocyte/macrophage activator) Platelet count WBC count Neutrophil count Erythrocyte sedimentation rate (ESR)

(Adapted, with permission, from K. Kalantar-Zadeh, Inflammatory marker-mania in chronic kidney disease: pentraxins at the crossroad of universal soldiers of inflammation, Clin J Am Soc Nephrol 2 (2007) 872-875.)

(WBC) count. These markers are, however, often nonspecific, as they can be affected by multiple other conditions. More specific markers of inflammation, such as CRP and IL-6 may offer a more unbiased assessment of the inflammatory cascade but are more expensive, and some of these tests are not readily available in clinical practice. To complicate matters further, direct measurement of some important elements of the inflammatory system, such as TNF-α and IL-1β or its circulating receptor antagonist (IL-1ra), may indeed be confusing, as plasma levels of these cytokines may not correlate well with their biological activities. However, serum IL-6 levels are in fact more useful as markers of IL-1β activation than IL-1 levels.[62] Furthermore, some circulating cytokines such as IL-10 are antiinflammatory, and their serum levels may exhibit no or reverse association with the severity of inflammation.[63] There is currently no single best test to assess inflammation in CKD for diagnostic purposes; although the emerging wider availability of a laboratory test for highly sensitive CRP, coupled with a large volume of epidemiological data showing the strong predictive value of a high CRP level for cardiovascular events and mortality make this test a plausible diagnostic tool to assess inflammation. The therapeutic application of certain antiinflammatory medications often warrants the measurement of specific markers (such as the use of B-cell depleting agents); unfortunately, this may in itself hinder the practical availability of such therapeutic modalities.

MALNUTRITION-INFLAMMATION COMPLEX

Protein-energy malnutrition (PEM), also referred to protein-energy wasting (PEW),[64] is present in a large proportion of patients with NDD-CKD and ESRD, and its markers such as low serum albumin, low protein intake, and diminished appetite, are strong predictors of hospitalization and mortality.[65–67] Among persons with CKD, the presence of an inflammatory state is often closely related to PEW; hence, in the nephrology literature this common clinical constellation has been referred to as the "malnutrition-inflammation cachexia (or complex) syndrome" (MICS) or "malnutrition-inflammation-atherosclerosis" (MIA) syndrome to emphasize its close link to atherosclerotic cardiovascular disease in CKD (Figure 13-3).[65,68,69] Several scoring systems have been proposed to assess the degree of MICS or MIA in dialysis patients, such as the malnutrition-inflammation score (MIS).[70] This correlates strongly with both measures of nutritional status and inflammation and anemia and also with hospitalization rates and mortality in hemodialysis patients.[70]

There is evidence to suggest that PEW is a consequence of chronic inflammatory processes in patients with CKD.[68,69] Although proinflammatory cytokines may be a common link between wasting disease and inflammation, additional factors such as oxidative stress, carbonyl stress, uremic toxins, and others may also play roles.[38,39] There is conflicting evidence regarding the direct role of chronic inflammation in engendering PEW in CKD. The hypothesis that PEW is a consequence of chronic inflammatory processes in patients with ESRD is supported by several lines of evidence:

1) Inflammation is associated with a rise in plasma levels and probably tissue levels of catabolic cytokines; plasma elevations of inflammatory proteins and catabolic cytokines are commonly observed in nondialyzed patients with advanced chronic renal insufficiency and in dialysis patients. One such cytokine, TNF-α, promotes catabolic processes (engendering both protein degradation and suppression of protein synthesis) and induces anorexia.[65,71]
2) Some dialysis patients with chronic inflammation develop weight loss and a negative protein balance, despite an intact appetite. In this setting, there may be a shift in protein synthesis from muscle to acute-phase proteins as renal function declines. Such patients also appear to lose more body weight during dialysis when compared to those without discernible inflammatory processes.[72]

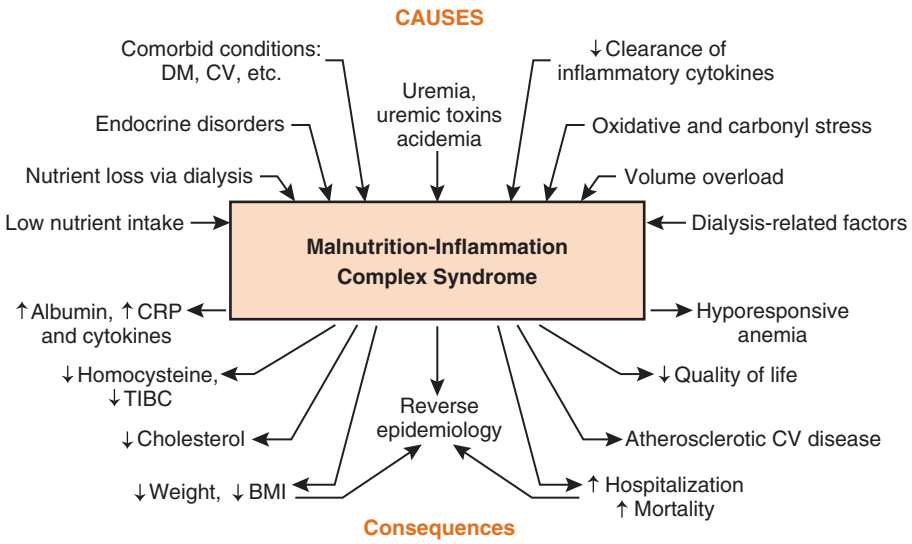


FIGURE 13-3 Schematic representation of the malnutrition inflammation complex (cachexia) syndrome (MICS). (Adapted from K. Kalantar-Zadeh, T.A. Ikizler, G. Block, et al: Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am. J. Kidney. Dis. 42 (2003) 864-881.)

3) Albumin synthesis is suppressed when serum CRP is elevated.[68] In CKD patients, serum albumin decreases and proinflammatory cytokines accumulate as renal function deteriorates.[32,34,73] Among well-dialyzed patients, activation of the acute phase response also correlates with lower serum albumin levels due to decreased albumin synthesis.[74]
4) Inflammation may lead to low serum cholesterol, which is a strong mortality risk factor in dialysis patients and a marker of poor nutritional status.[75] This was best shown in a prospective study of 823 patients who were categorized by either the presence or absence of inflammation and malnutrition, which was defined by a low serum albumin concentration or elevated levels of CRP or IL-6. Among all patients, including those with inflammation, lower cholesterol levels were associated with higher mortality. By comparison, higher cholesterol levels in those without markers of inflammation and malnutrition were associated with higher mortality.[75]

There is, however, also evidence that does not support inflammation as the principal cause of PEM:

1) Serum albumin and prealbumin levels and other markers of nutritional status obviously correlate with protein intake independent of inflammatory status.[76] The serum albumin decreases only modestly among normal individuals with PEW induced by reducing their nutrient intake or in malnourished hemodialysis patients fed low protein diets, suggesting that serum albumin is a direct reflection of protein intake.[77,78]
2) In dialysis patients, the association of serum albumin and CRP is hardly precise, with the reported correlation coefficients usually being less than 0.50.[77,79]
3) Unlike serum CRP levels, serum albumin concentrations usually do not fluctuate on a month-to-month basis.[80]
4) In some studies, the provision of adequate nutrition without management of inflammation improves hypoalbuminemia and clinical outcome.[81,82]

These considerations, although not conclusive, indicate that factors other than the catabolic consequences of inflammation (such as nutrient intake) also affect serum albumin and other nutritional measures. Interestingly, there are also data suggesting that malnutrition itself can be a cause, rather than a consequence of inflammation:

1) Malnourished dialysis patients may be deficient in antioxidants such as vitamin C or carotenoids,[43] which may lead to increased oxidative stress and inflammation.
2) PEM may decrease host resistance and predispose to infection, which is clearly an inflammatory disorder. Certain nutrients, such as arginine and glutamine, may enhance the immune response.[83] Moreover, preliminary data suggest that levocarnitine may protect against endotoxins and also may suppress elaboration of TNF-α from monocytes.[84]
3) Hypocholesterolemia, as a reflection of general hypolipoproteinemia in malnourished dialysis patients, may mitigate the ability to remove circulating endotoxins. Based upon the lipoprotein-endotoxin hypothesis, there is an optimum serum lipoprotein concentration below which lipid reduction is detrimental because of the decreased ability of lipoproteins to bind lipopolysaccharide; this, in turn, may prevent lipoproteins from decreasing the detrimental effects of endotoxin.[85]

Moreover, prospective cohort studies have shown that higher levels of CRP and IL-6 are associated with poor appetite in dialysis patients (Figure 13-4, *A* and *B*).[86,87] Nevertheless, it is not clear whether anorexia is the consequence of inflammation or whether poor protein intake in the setting of diminished appetite lead to inflammation. In summary, inflammation and PEW appear to be closely interrelated in CKD and ESRD, although their individual effects are complex and involve mechanisms of action that are not unrelated to each other.

CONSEQUENCES OF INFLAMMATION IN CHRONIC KIDNEY DISEASE

Clinical Outcomes in End-Stage Renal Disease

Epidemiological studies have fairly consistently reported a modest to strong association between levels of inflammatory markers and adverse outcomes such as morbidity,

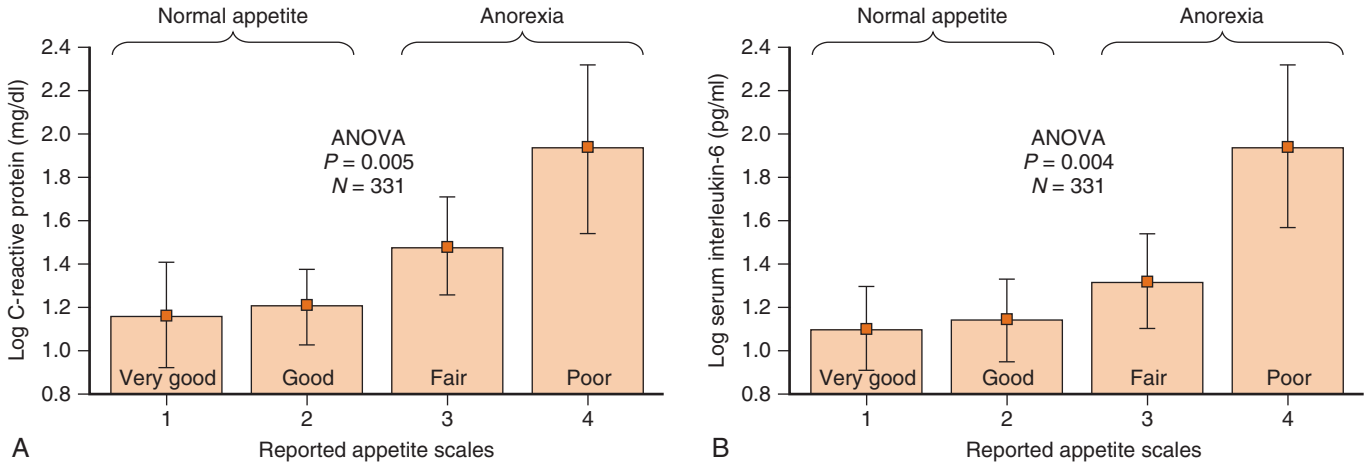


FIGURE 13-4 Anorexia is associated with higher serum CRP (**A**) and interleukin-6 (**B**) levels in 331 maintenance hemodialysis patients. (Adapted from K. Kalantar-Zadeh, G. Block, C.J. McAllister, et al: Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am. J. Clin. Nutr. 80 (2004) 299-307.)

hospitalizations, and cardiovascular and all-cause mortality in ESRD.[88–92] Poor outcomes have been associated with low serum albumin levels, elevated CRP, and proinflammatory cytokine levels in ESRD patients.[68,93] Most individuals with CKD and ESRD die of cardiovascular diseases (CVD). Thus, the purported link from underlying inflammation to decreased survival among renal patients, if it exists, should be most strongly observed for inflammation and atherosclerosis. Perhaps the best evidence supporting the importance of inflammation in the pathogenesis of atherosclerosis comes from the observation among patients without kidney disease that markers of increased systemic inflammation are directly associated with an enhanced risk of atherosclerosis. Although the evidence is less clear, ESRD patients with coronary heart disease and enhanced cardiovascular risk and mortality frequently have similar elevated levels of acute phase reactants.[92]

Clinical Outcomes in Predialysis Chronic Kidney Disease

Increasing clinical evidence also suggests that inflammation and oxidative stress are also associated with adverse outcomes among NDD-CKD patients.[94–96] This was perhaps best shown in a prospective study of 80 nondiabetic NDD-CKD patients in which the effect of different conventional and nonconventional risk factors on cardiovascular events was examined.[97] At follow-up at a median period of 7 years, 21 patients developed adverse outcomes due to coronary, cerebral, or peripheral artery occlusion. Upon multivariate analysis, an adverse cardiovascular outcome was independently associated with increased age, elevated CRP and fibrinogen, and advanced oxidation protein product levels. In addition to increased mortality, inflammation may also be associated with more rapid loss of kidney function in predialysis patients. This has been shown in posthoc analyses of the Cardiovascular Health Study and the Cholesterol and Recurrent Events study, in which higher levels of inflammation were associated with steeper slopes of serum creatinine and estimated glomerular filtration rate (eGFR).[98,99] These results were not corroborated by a similar posthoc analysis of the Modification of Diet in Renal Disease (MDRD) study, in which levels of CRP and leptin were not associated with slopes of eGFR.[100] A recent cohort study in 1220 patients found that in NDD-CKD patients, higher white blood cell count and lower serum albumin are associated with increased mortality (Figure 13-5, *A* and *B*). (Kovesdy et al, 2009) Indeed, in this study, a higher number of abnormal biomarkers (white blood cell count >7500/ml, % lymphocyte as a nutritional marker of <22% and serum albumin <3.6 g/dl) was incrementally associated with worse survival (Figure 13-6).

Other Outcomes

In addition to atherosclerosis, inflammation may have other adverse effects in renal disease such as refractory anemia, laboratory signs of iron overload, or poor quality of life.[101,102] Inflamed dialysis patients frequently display increased serum ferritin, which is a positive acute phase reactant and an indicator of increased iron burden.[103,104] Serum ferritin levels correlate with hospitalization rates, and an increase in serum ferritin concentration may be associated with an enhanced risk of death in hemodialysis patients[103] and in patients with predialysis CKD.[105]

INFLAMMATION AND ATHEROSCLEROSIS: ASSOCIATION VERSUS CAUSALITY

At present, most of the evidence implicating inflammation in adverse clinical outcomes in CKD is epidemiological, which does not allow the establishment of a cause–effect relationship. Nevertheless, the consistency of the observational studies is remarkable, and the involvement of inflammation in the process of atherosclerosis is biologically

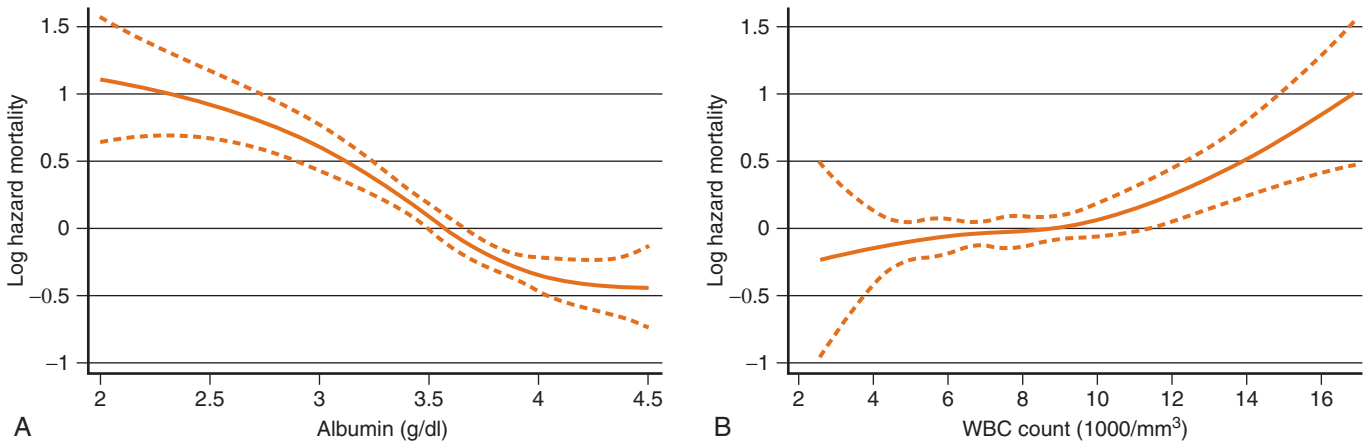


FIGURE 13-5 Multivariable adjusted hazards ratios (95% confidence intervals) of all-cause mortality associated with baseline serum albumin (**A**) and blood white blood cell count (**B**) levels in Cox models adjusted for age, race, Charlson comorbidity index, diabetes mellitus, cardiovascular disease, smoking, systolic and diastolic blood pressure, body mass index, eGFR, serum calcium, phosphorus, hemoglobin, bicarbonate, cholesterol, and 24-hour urine protein. Adapted from C.P. Kovesdy, S.M. George, J.E. Anderson, K. Kalantar-Zadeh, Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease, Am. J. Clin. Nutr. 90(2) (2009) 407-414.

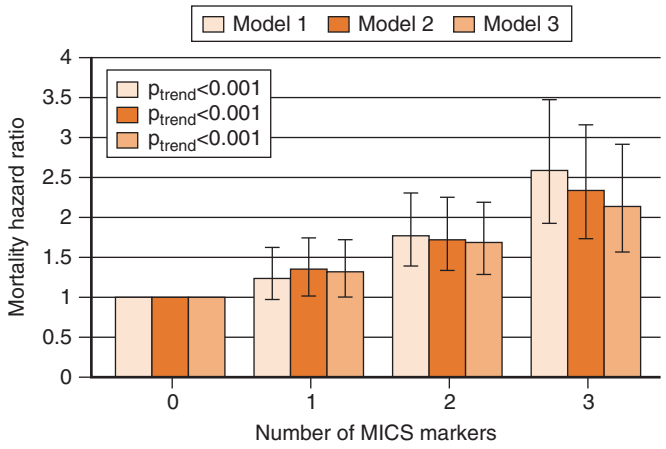


FIGURE 13-6 Hazard ratio (95% confidence intervals) of all-cause mortality in 1220 patients with nondialysis-dependent CKD, categorized according to the number of concomitantly present markers of protein-energy wasting in time-dependent Cox models. Markers of protein-energy wasting was defined as serum albumin less than 3.7 g/dl, percentage of lymphocytes in white blood cell count less than 22%, and white blood cell count greater than 7500/mm^3 Model 1: unadjusted; Model 2: adjusted for age, race, Charlson comorbidity index, diabetes mellitus, cardiovascular disease, smoking, systolic and diastolic blood pressure; Model 3: adjusted for Model 2 variables plus body mass index, eGFR, serum calcium, phosphorus, hemoglobin, bicarbonate, cholesterol, and 24-hour urine protein. Adapted from C.P. Kovesdy, S.M. George, J.E. Anderson, K. Kalantar-Zadeh, Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease, Am. J. Clin. Nutr. 90(2) (2009) 407-414.

plausible, because the cellular and subcellular mechanisms whereby inflammation induces and promotes atherosclerosis are now established.[106] Given the complexity of the inflammatory cascade, it is unclear, though, which inflammatory molecules are causally involved in the process of atherosclerosis and which ones are merely "tagging along" in the process (Figure 13-7). Such detailed knowledge of the role of various inflammatory mediators is important, because it may affect therapeutic intervention meant to prevent the adverse outcomes related to inflammation. Studies of Mendelian randomization suggest that CRP, although an excellent marker of inflammation and a consistent prognostic indicator of adverse outcomes, is not causally related to de novo development of atherosclerosis in the general population[107] or in patients with ESRD.[108] The role of CRP in initiating atherosclerosis is also questioned by studies in transgenic mice.[109–111] It is possible, though, that CRP plays a role in aggravating the impact of atherosclerosis on clinical outcomes, as it was found that blocking the complement-activating effect of CRP led to significantly less severe tissue injury in a rat model of myocardial infarction.[112] Much less information is available on the causal role of other inflammatory mediators. Based on Mendelian randomization studies in ESRD patients, it is possible that TNF-β and IL-6 play a causal role in the initiation of atherosclerosis.[113,114]

PHARMACOLOGICAL THERAPY OF INFLAMMATION

Based on the possible causal link between inflammation and the adverse clinical events linked to it, it is quite possible, although not yet conclusively proven, that an alleviation of inflammation could improve clinical outcome in CKD patients. Moreover, because the deleterious effect of inflammation is usually exerted within a short period it is possible that short-term interventions would suffice to reverse the inflammation and improve survival. Unfortunately (but not surprisingly) clinical trials to prove this hypothesis have not yet been performed. Opposite to disease states involving short-term outcomes (such as rheumatological diseases, where the endpoint can be symptomatic improvement),

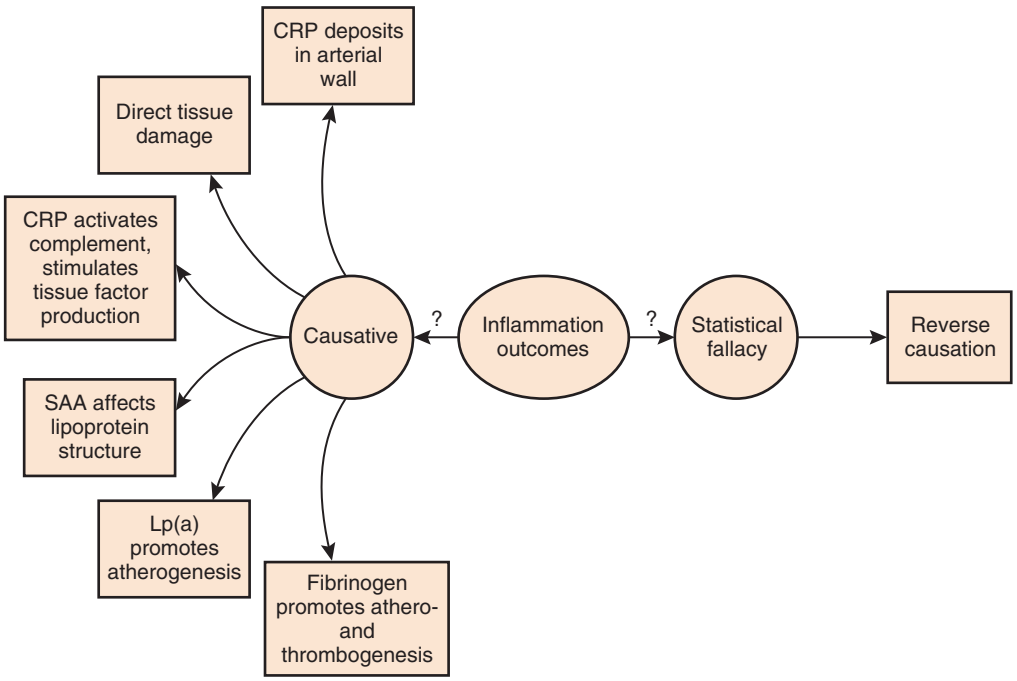


FIGURE 13-7 Potential explanations for the association between chronic inflammation and adverse outcomes in epidemiological studies.

a meaningful endpoint in CKD is mortality or some other relevant clinical event, and it will take large numbers of participants and much longer studies to prove therapeutic benefits from any antiinflammatory intervention. Another impediment is the balance between risks and benefits in such studies, as the use of antiinflammatory agents that have potent immune suppressing capabilities can be complicated by dangerous complications. Nevertheless, the potential upside of successful antiinflammatory therapies in patients with CKD and ESRD is significant, given the failure of conventional treatment modalities to achieve meaningful improvement in their outcomes.

The complexity of the inflammatory system has facilitated the development of a remarkably diverse array of antiinflammatory agents. Most of these agents have not been studied in patients with CKD, but will be discussed here nevertheless (Table 13-3), because clinical application of any of these agents in CKD is possible in the future. Possible goals of

TABLE 13-3 Antiinflammatory Pharmacological Therapies

TARGET	AGENT	STRUCTURE	MECHANISM OF ACTION	APPROVED INDICATIONS	USE IN CKD
TNF	Etanercept (Enbrel®, Amgen, and Wyeth Pharmaceuticals)	Two p75 TNF receptors bound to the Fc portion of IgG soluble TNF receptor	Binds TNF	Rheumatoid arthritis, ankylosing spondylitis, psoriasis	Phase II trial in ESRD underway
	Onercept (Serono)	p55 soluble TNF receptor	Binds TNF	None yet; Phase III trial for psoriasis discontinued for safety reasons	None
	Infliximab (Remicade®, Centocor)	Chimeric monoclonal antibody	Binds TNF	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease	None
	Adalimumab (Humira®, Abbott Laboratories)	Humanized monoclonal antibody	Binds TNF	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn disease	None
	Certolizumab (UCB Pharma Ltd.)	Pegylated Fab fragment of a humanized monoclonal antibody	Binds TNF	None yet; tested in Crohn disease and psoriasis	None
	Thalidomide (Thalidomid®, Celgene Corp.)	Alpha-(N-phthalimido) glutaramide	Decreases the transcription of TNF (immunomodulatory)	Chemotherapy, erythema nodosum leprosum, HIV wasting	None
	Lenalidomide (Revlimid®, Celgene Corp.)	Thalidomide analogue	Immunomodulator	Chemotherapy	None
	Pentoxifylline (Trental®, Sanofi-Aventis)	1-(5-oxohexyl)-3, 7-dimethylxanthine	Nonspecific phosphodiesterase inhibitor; inhibits TNF transcription	No antiinflammatory indication.	None; tested in clinical trials*
	CF101 (Can-Fite BioPharma)	?	A3 adenosine receptor agonist; inhibits TNF transcription	None yet, tested in Phase I and II trials for rheumatoid arthritis and cancer	None
	TMI-1	4-[[4-(2-butynyloxy) phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-(3S) thiomorpholine carboxamide	Dual TNF-converting enzyme/ matrix metalloprotease inhibitor	None yet; studied in rheumatoid arthritis	None
IL-1β	Anakinra (Kineret®, Amgen)	Human recombinant IL-1 receptor antagonist	Competitively inhibits IL-1 binding to IL-1 receptor	Rheumatoid arthritis	None**
	Rilonacept (Regeron Pharmaceuticals)	Fusion protein of human cytokine receptor extracellular domains and the Fc portion of human IgG1	IL-1 trap	None yet; pending indication for cryopirin-associated periodic syndromes	None
	Pralnacasan (Vertex Pharmaceuticals)	Ethyl-hemiacetal prodrug	IL-1 converting enzyme inhibitor. May also inhibit production of IL-18	None; Phase IIB trial in rheumatoid arthritis suspended due to toxicity	None

Continued

TABLE 13-3 Antiinflammatory Pharmacological Therapies—cont'd

TARGET	AGENT	STRUCTURE	MECHANISM OF ACTION	APPROVED INDICATIONS	USE IN CKD
IL-6	Tocilizumab (Actemra®, Roche/Chugai)	Humanized monoclonal antibody	Blocks IL-6	None in the U.S.; approved in Japan for Castleman disease; Phase III trials completed in rheumatoid arthritis	None
CTLA-4	Abatacept (Orencia®, Bristol-Myers Squibb)	Soluble fusion protein comprising CTLA-4 and the Fc portion of IgG1	Prevents CD28 from binding to CD80/CD86 (costimulatory blocker)	Rheumatoid arthritis	None
CD20	Rituximab (Rituxan®, Genetech and Biogen Idec)	Monoclonal anti-CD20 antibody (both mouse and human portions)	B cell depletion through multiple antibody-dependent mechanisms	Non-Hodgkin lymphoma, rheumatoid arthritis	Studied in various glomerular diseases
IL-15	HuMax-IL 15 (Genmab A/S)	Recombinant human antibody against IL-15	Binds IL-15	None; studied in phase I/II trials for rheumatoid arthritis	None
IL-18	rhIL-18	Recombinant human antibody against IL-18	Binds IL-18 and blocks induction of IFN-gamma and other cytokines	None; studied in rheumatoid arthritis	None
NF-κB	Pioglitazone (Actos®, Takeda Pharmaceuticals America) and Rosiglitazone (Avandia®, GlaxoSmithKline)	Thiazolidinediones	PPAR-γ agonists; decrease production of NF-κB and increases inhibitor-κB levels. May also have other mechanisms of action	Diabetes mellitus; no antiinflammatory indication	None. Reduced CRP levels in a study of patients on peritoneal dialysis
COX	NSAIDs (multiple)	Various	Inhibition of cyclooxygenase and lipoxygenase and reduction of prostaglandin synthesis	Various acute and chronic conditions associated with inflammation	None
Complex	Bardoxolone methyl		Antioxidant inflammation modulator	None yet; possible future indications in oncology and nephrology	Phase II clinical trial in progress testing effect on eGFR in diabetic nephropathy
Uncertain	Statins (multiple)	Various	Hydroxymethylglutaryl-Coenzyme A inhibitors. But antiinflammatory effect may be unrelated to cholesterol lowering	Cholesterol lowering; no antiinflammatory indication	None; effect on outcomes tested in clinical trials
Uncertain	ACE-inhibitors/Angiotensin receptor blockers (multiple)	Various	Decrease lipopolysaccharide-stimulated production of multiple cytokines	Antihypertensive; no antiinflammatory indication	Antihypertensive; no antiinflammatory indication
Uncertain	Sevelamer hydrochloride (Renagel®, Genzyme Corp.)	Cationic polymer	Binds phosphorus and other molecules in the intestinal tract. Potentially antiinflammatory mechanisms include the reduction of low molecular weight uremic toxin levels or a direct effect on arterial wall calcification	Phosphate binder; no antiinflammatory indication	Phosphate binder in ESRD
Uncertain	Heparin (generic)	Glycosaminoglycan formed by repeated sulphated oligosaccharide units	Possible antiinflammatory mechanism involves attenuation of CD11b dependent leukocyte adherence. Other mechanisms possible	Anticoagulant; no antiinflammatory indication	Anticoagulant; no antiinflammatory indication
Uncertain	Megestrol acetate (Megace®, Bristol-Myers Squibb and Par Pharmaceuticals)	Synthetic derivative of progesterone	Downregulation of IL-1, IL-6, and TNF	Appetite stimulant; no antiinflammatory indication	None; studied in trials of nutritional status in ESRD

(Adapted from C.P. Kovesdy, K. Kalantar-Zadeh, Novel targets and new potential: developments in the treatment of inflammation in chronic kidney disease, Expert Opin. Investig. Drugs 17 (2008) 451-467.)
*At least one clinical trial is currently in process and registered at www.clinicaltrial.gov.
**Phase II clinical trial in progress.

antiinflammatory interventions could be to address relatively well-circumscribed conditions, such as certain types of glomerulonephritides (vide infra), or as a more general approach to alleviate systemic inflammation, with an eye toward improving first surrogate outcomes (such as serum CRP, albumin, or other markers of nutrition), then morbidity (such as progression of CKD and various cardiovascular disease states), and finally mortality.

Interleukin-1 Inhibition

IL-1 is a multifunctional cytokine that plays a central, "housekeeping" role in the inflammatory reaction.[62] Various approaches to IL-1 inhibition have been used.

A. Interleukin-1 Receptor Antagonist (IL-1Ra)

The agonist effects of IL-1 are partially regulated by IL-1Ra, which is a naturally occurring glycoprotein inhibitor that binds the high affinity cell surface IL-1 receptor without activating it, and thus it competes with the active IL-1 molecule for binding sites (see Figure 13-1).[115] The effects of IL-1Ra include decreased prostaglandin production, decreased matrix metalloproteinase production, and reduction in the infiltration tissues by mononuclear cells.[116–118] Anakinra is a human recombinant IL-1Ra that is available for treatment of rheumatoid arthritis (RA), and it may also be useful in treating other rheumatic disorders such as Still disease. It differs from the native human protein in that it is not glycosylated and it has an additional N-terminal methionine. Anakinra may also show promise in the treatment of inflammation in patients with CKD. To date, a single study has been conducted regarding the pharmacokinetics of this drug in patients with impaired renal function.[119] Anakinra (1 mg/kg IV) was given to 12 patients with normal renal function, and 20 patients on hemodialysis. Another arm of this study evaluated subcutaneous administration of 100 mg of anakinra to five groups of patients stratified according to varying degrees of renal function ranging from normal to ESRD. This study demonstrated that the main route of elimination for Anakinra is renal clearance, and that hemodialysis has a very small effect on clearance. As a result of this study, thrice weekly dosing of anakinra may be possible.

B. Interleukin-1 "Trap"

Cytokine traps are high-affinity blockers of cytokine action that may be more potent inhibitors than other agents.[120] IL-1 is among the first cytokines targeted by this approach. Rilonacept is an IL-1 trap that incorporates two signaling chains of the cell surface IL-1 receptor linked by the Fc portion of IgG1 to form a soluble IL-1 binding protein with high affinity.[121] This agent is in clinical trials in children with juvenile idiopathic arthritis and in adults with RA. It has not yet been studied in patients with CKD.

C. Interleukin-1β–Converting Enzyme Inhibition

IL-1β–converting enzyme (ICE) inhibition reduces cytokine production by inhibiting posttranslational protein processing.[62] ICE cleaves the inactive precursor of IL-1β into an active molecule, and ICE inhibition could decrease the release of biologically active IL-1. This approach could also reduce the synthesis of IL-18, which is a cytokine that is part of the IL-1 superfamily that also has pleiotropic effects. TNF is also produced though a pathway that may be amenable to a similar approach. An oral ICE inhibitor, pralnacasan, was studied in animal models.[122,123] In preliminary human studies antiinflammatory effects were present; diarrhea and nausea were the most frequently reported adverse effects. A phase IIB clinical trial of pralnacasan in patients with RA was suspended due to hepatotoxic effects in animals that received the drug for several months. It is unlikely that this agent will be tested in CKD.

Interleukin-6 Inhibition

IL-6 has both proinflammatory and antiinflammatory effects (see Figure 13-1).[124] Its roles are also multiple: it can activate T cells, B cells, macrophages, and osteoclasts, and it is a pivotal mediator of the hepatic acute-phase response. IL-6 binds to both soluble and membrane-bound receptors and leads to the transduction of intracellular signals, mediating gene activation and a wide variety of biological activities.[125] Tocilizumab is a humanized antihuman IL-6 receptor antibody of the IgG1 subclass made by grafting a mouse antihuman IL-6 receptor monoclonal antibody onto human IgG1. Tocilizumab competes for both the membrane-bound and soluble forms of human IL-6 receptor, thus inhibiting the binding of the native cytokine to its receptor and interfering with the cytokine's effects. Clinical trials with tocilizumab indicate that this medication could be an effective agent for the treatment of both RA and juvenile RA.[126,127] We are not aware of plans to use this medication in CKD.

Tumor Necrosis Factor-α Inhibition

A "multifunctional" cytokine, TNF-α has attracted significant attention in the process of antiinflammatory drug development, with several agents approved for various indications and many more in the development process. The exact mechanism of action whereby the inhibition of TNF-α exerts a beneficial effect in diseases characterized by inflammation is likely multifactorial, given the broad role of TNF-α in the inflammatory reaction.[128] Processes that TNF-α is involved in include endothelial cell activation, angiogenesis, the induction of various metalloproteinases and adhesion molecules, and the modulation and regulation of other inflammatory cytokines.

A. Blockers of the Tumor Necrosis Factor-α Molecule

Several TNF-α blockers (etanercept, infliximab, adalimumab and certolizumab) are approved for the treatment of various rheumatic diseases by the United States Food and Drug Administration (FDA); others are undergoing development.

1) **Etanercept** is a soluble p75 TNF-α receptor fusion protein that consists of two p75 TNF receptors bound to the Fc portion of IgG. One etanercept molecule binds two TNF molecules. Etanercept is effective for the treatment of various forms of inflammatory arthritis like RA, psoriatic arthritis, and ankylosing spondylitis. It is

administered once or twice weekly via subcutaneous injection. The effectiveness of etanercept in improving the nutritional status and clinical outcomes of hemodialysis patients as a consequence of its antiinflammatory properties is being studied in a Phase II randomized, double-blind, placebo-controlled clinical trial (www.clinicaltrials.gov identifier: NCT 00293202). The primary outcome measure of this study is serum albumin and CRP levels.

2) **Onercept** is a p55-soluble TNF-α receptor that has been studied in clinical trials of patients with inflammatory bowel disease, psoriasis, and psoriatic arthritis.[129] Due to an unfavorable risk-benefit profile, however, the manufacturer of onercept has recently discontinued three phase III clinical trials in patients with moderate-to-severe psoriasis. It is unclear what the future fate of this agent will be. There are no plans for studies in CKD.
3) **Infliximab** is a chimeric monoclonal antibody directed against TNF-α. The antigen-binding portion of infliximab is murine, and the constant Fc domain is human. Infliximab is administered via intravenous infusion approximately once every 6 weeks. Infliximab is effective for the treatment of a number of forms of inflammatory arthritis, inflammatory bowel disease, and other conditions. There are no plans for studies in CKD.
4) **Adalimumab** is a humanized monoclonal antibody that is administered subcutaneously once every 2 weeks. Due to its humanized construction, adalimumab is associated with a lower risk of antidrug antibody formation compared with infliximab. Adalimumab has been approved for use in RA, psoriatic arthritis, ankylosing spondylitis, and Crohn disease. There are currently no plans for studies in CKD.
5) **Certolizumab** pegol consists of the pegylated Fab fragment of a humanized monoclonal antibody that is directed against TNF and has been tested in Crohn disease.[130,131] Unlike infliximab and adalimumab, certolizumab does not contain an Fc portion; hence, it is devoid of complement activation, antibody-dependent cellular cytotoxicity, or apoptosis. It is unclear what the practical advantages of this difference will be. Certolizumab is subcutaneously injected once a month. No application in CKD is planned.

B. Inhibitors of Tumor Necrosis Factor-α Gene Transcription

1) **Thalidomide**, a once-popular antiemetic agent, exerts an immunomodulatory effect by decreasing the transcription of TNF-α and the stability of its mRNA. The usefulness of this agent is limited by its toxicities, including teratogenicity. There are currently no studies of thalidomide in CKD.
2) **Lenalidomide** is an analogue of thalidomide that promises greater potency without a teratogenic potential. Currently it is being studied as a potential treatment for multiple myeloma and myelodysplasia.[132] It is unclear if this agent will see an application in the treatment of chronic inflammation, including in CKD.
3) **Pentoxifylline** is a nonspecific phosphodiesterase inhibitor that inhibits TNF transcription and was found beneficial in the treatment of arthritis in experimental animals.[133] In a number of small clinical trials of RA, it did not produce meaningful benefits and was marred by poor tolerance.[134–136] Pentoxifylline will be tested in ESRD patients in a randomized, double-blinded, placebo-controlled clinical trial (www.clinicaltrials.gov Identifier: NCT00561093). The Anti-Inflammatory and Anti-Oxidative Nutrition in Dialysis Patients (AIONID) study is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and will examine the effect of oral nutritional supplements with antiinflammatory and antioxidant properties along with pentoxifylline therapy in a factorial design on malnutrition and inflammation in 100 patients receiving maintenance hemodialysis.
4) **CF101** is an A3 adenosine receptor agonist that has antiinflammatory effects and reduced production of TNF in animal models.[137] Inhibition of transcription of TNF is a characteristic of adenosine.[138] Adenosine agonists in humans may be limited by dose related adverse effects: flushing, tachycardia, nausea, vomiting, and leukocytosis have been reported.[139] This agent has not been studied in CKD.

C. Agents Using Other Mechanisms to Inhibit Tumor Necrosis Factor-α

TMI-1 is a dual TNF-α converting enzyme/matrix metalloproteinase inhibitor that is under investigation in RA.[140] Theoretically, although this agent may reduce secretion of TNF-α, it could allow membrane expression of it, which could be pathogenically important. Clinical trial data should answer such concerns; to date TMI-1 has not been studied in CKD.

Costimulation Blockade

The activation of T cells by antigen presenting cells requires two signals: binding of the T cell receptor-peptide-major histocompatibility (MHC) II complex and binding of cell surface costimulatory molecules that provide the essential "second signal."[141-143] Two major costimulatory systems are described: CD28 and/or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) that can bind to one of two other proteins, CD80 or CD86 (often referred to as B7-1/B7-2),[142] and CD40, which binds to CD154 (also known as CD40 ligand, CD40L, or gp39).[141] Abatacept (also called CTLA4-Ig) is a soluble fusion protein comprising CTLA-4 and the Fc portion of IgG1. It prevents CD28 from binding to CD80 or CD86, due to its higher affinity for CD28. Administration of CTLA4-Ig prevents or ameliorates collagen-induced arthritis in mice and is beneficial in transplantation models.[144,145] Abatacept is approved for use in RA. It is unclear if there are plans for its use in CKD.

B Cell Depletion

B cell depletion is emerging as a new therapeutic approach in a variety of inflammatory conditions. Lymphocytes of the B cell lineage express on their surface CD20, a B lymphocyte-specific molecule; this is lost as B cells differentiate into plasma cells. Rituximab is a B cell– depleting monoclonal anti-CD20 antibody, made up of both mouse and human parts. Rituximab causes B cell depletion and may do so through a variety of antibody-dependent mechanisms.[146] By virtue of the absence of CD20 protein expression on their

surface, plasma cells are resistant to rituximab. As a consequence of this, immunoglobulin levels remain within the normal range, despite profound B cell depletion that persists for several months following a single course of treatment.

Levels of autoantibodies with important roles in the pathophysiology of specific diseases such as rheumatoid factor in RA,[147,148] anti-dsDNA antibodies in systemic lupus erythematosus,[149] and antineutrophil cytoplasmic antibodies (ANCA) in ANCA-associated vasculitis[150–152] are, however, affected by B cell depletion. Rituximab may thus hold promise as a therapeutic agent in several immune-mediated conditions, and it has been examined for the treatment of various glomerular diseases.[153–157] It is unclear if this agent will be employed for the treatment of chronic inflammation in CKD, because the autoantibody depletion resultant after B cell depletion may be more specific to certain types of diseases.

Interleukin-15 Inhibition

IL-15 is an innate response cytokine that mediates a broad range of effects including activation of T cells, B cells, natural killer cells, and neutrophils. It also regulates cell survival and protects various cell types from apoptosis, and it may facilitate angiogenesis.[158] HuMax-IL15 is a fully human antibody that is capable of binding both soluble and membrane-bound IL-15. HuMax-IL15 is currently in phase I/II clinical trials in patients with RA. This agent appears to be well–tolerated, and it produced encouraging responses after 4 or 8 weeks of therapy in RA.[159] Adverse events reported were flulike symptoms, transient fever, myalgia, upper respiratory tract infection, herpes simplex viral infection, and aphthous stomatitis. Larger studies are awaited; it is unclear if this agent will be used in CKD.

Interleukin-18 Inhibition

IL-18 has multiple roles, including mediation of interferon-γ production, IL-8 release, and nuclear factor-kappa-B (NF-κB) mediated transcription of inflammatory cytokines. A recombinant human IL-18 binding protein was identified that effectively blocked these effects of IL-18 in vitro.[160] Recombinant human IL-18 binding protein is being studied for potential efficacy and safety in the treatment of RA;[161] it is unclear if this agent has the potential to be used in CKD in the future.

Agents with Complex or Unclear Mechanisms of Action

Opposite to the previously described "designer" agents, several medications have been found to have antiinflammatory properties while being used for different primary indications.

A. Peroxisome Proliferator-Activated Receptor-Gamma Agonists

Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ), a member of the nuclear receptor superfamily of ligand-activated transcription factors, is highly expressed in atherosclerotic plaques.[162,163] The agonists of this receptor in clinical use are the thiazolidinediones rosiglitazone and pioglitazone. These agents have insulin-sensitizing actions and are used in the treatment of type II diabetes. Accumulating evidence suggests that PPAR-γ agonists may have inhibitory effects on inflammatory processes in atherosclerotic plaques through indirect (insulin-sensitizing) and direct mechanisms.

One important molecular target of PPAR-gamma agonism is the transcription factor NF-κB, which controls the synthesis of many proinflammatory genes.[164–167] Rosiglitazone has been shown to possess an antiinflammatory effect in vitro[168,169] and in animal models.[170] An antiinflammatory and antioxidant effect of rosiglitazone would be of potential benefit in conditions such as atherosclerosis, which is characterized by a chronic inflammation of the arterial wall.[106]

Troglitazone,[171] an agent that was withdrawn from the market due to hepatotoxicity, and pioglitazone[172] have also been shown to reduce carotid arterial intimal-medial thickness; this phenomenon could be related causally to an antiinflammatory effect of thiazolidinediones. Rosiglitazone caused suppression of intranuclear content of NF-κB in mononuclear cells and the plasma concentrations of CRP and monocyte chemotactic protein (MCP)-1 in a nonrandomized study of both nondiabetic and diabetic subjects,[173] and it reduced serum CRP levels in randomized, double-blind, placebo-controlled studies of diabetic[174] and nondiabetic[175] patients. Rosiglitazone also reduced insulin requirements and CRP levels in diabetic patients with ESRD on peritoneal dialysis.[176] There are no studies a priori examining the effect of PPAR-γ agonists on hard clinical endpoints such as mortality in patients with CKD.

B. Nonsteroidal Antiinflammatory Drugs

Nonsteroidal Antiinflammatory Drugs (NSAIDs) are one of the most commonly used drug classes worldwide; they are used by over 17 million Americans on a daily basis. The main mechanism of action of NSAIDs is the inhibition of cyclooxygenase, whereby they impair the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes.[177] Nonprostaglandin effects have been postulated to explain certain effects seen with NSAIDs; these include a decrease in the expression of L-selectin and thus an inhibition of neutrophils-endothelial adherence,[178] and the in vitro inhibition of NF-κB dependent transcription with consequent inhibition of inducible nitric oxide synthetase.[179] The latter effect is characteristic of aspirin at therapeutic doses; other NSAIDs require supratherapeutic doses to achieve the same effect.[179] A novel prostaglandin-mediated effect of NSAIDs is the inhibition of apoptosis; this may explain observations finding an association between aspirin use and a lower incidence of colorectal cancer.[180] It is unclear if NSAIDs will ever be explored in CKD for the alleviation of chronic inflammation with the goal of improving mortality. The adverse impact on kidney function in patients with CKD who are not yet on dialysis makes this very unlikely. Furthermore, the recent withdrawal of rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor due to increased risk of cardiovascular events highlights the potential pitfalls of such an approach.

C. Hydroxymethylglutaryl-Coenzyme A Inhibitors (Statins)

Statin drugs are usually employed to lower blood cholesterol level, but their effects appear to go beyond cholesterol-lowering and include an antiinflammatory mechanism. In studies of primary and secondary cardiovascular prevention, statins were found to lower serum CRP concentration as early as 14 days into therapy, independent of their lipid-lowering effects.[181–184] Patients with RA who were given atorvastatin in a clinical trial experienced symptomatic improvement and the reduction of CRP.[185] At least some of the cardiovascular benefits seen with statin therapy are now being attributed to their antiinflammatory effect. Different statins may have different antiinflammatory potency.[186] The mechanism of action of the statins' antiinflammatory nature is not fully understood; it may involve the inhibition of the main β-2 integrin lymphocyte function-associated antigen (LFA)-1 and thus the impairment of inflammatory cell adhesion,[187,188] or reduced lipidation of intracellular proteins and reduced expression of major histocompatibility complex II molecules on antigen-presenting cells with subsequent decrease in T-lymphocyte activation.[189] The use of statins for antiinflammatory purposes in CKD is an intriguing possibility. The negative findings of two large clinical trials (the 4D study and the Die Deutsche Diabetes Dialyse Studie (the 4D study) and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) study) that examined the effect on mortality and cardiovascular events of statin therapy versus placebo in dialysis patients are disappointing from this standpoint.[190,191] Another large clinical trial examining statin therapy in patients with various stages of CKD is being conducted,[192] which should provide further evidence for or against the usefulness of statins in this patient population, including answers regarding the role of their antiinflammatory effects.

D. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin receptor blocker (ARB) medications are used primarily for blood pressure lowering purposes, but they have been found to exert a beneficial impact on outcomes in pathological states such as congestive heart failure (CHF) and CKD. The benefits seen in such conditions may be related to mechanisms different from their antihypertensive effect. One such potential mechanism is an antiinflammatory effect. In one study of patients with CHF, high dose enalapril reduced IL-6 levels, with a concomitant decrease in the thickness of the interventricular septum.[193] In another short-term study of patients with CHF, the use of candesartan reduced plasma levels of TNF-α, IL-6, and vascular adhesion molecules.[194] ACE inhibitors have also shown antiinflammatory properties in the general population and in patients with CKD.[195,196] These classes of medications could thus be used as an a priori therapy against chronic inflammation in CKD, especially because their well-established benefits in other areas should mitigate fears about potential deleterious effects. We are unaware of any current clinical trials testing this hypothesis though.

E. Sevelamer Hydrochloride

Sevelamer hydrochloride is a cationic polymer that is currently being used in patients with ESRD as an intestinal phosphate binder. This agent also possesses several "pleiotropic" effects that are unrelated to its original clinical indication; one such effect may be the amelioration of inflammation. A lowering of CRP levels was seen with the use of sevelamer hydrochloride in some,[197,198] but not all studies.[199] One proposed mechanism of action for an antiinflammatory effect of sevelamer hydrochloride is the decrease in calcium phosphate microcrystal depositions in the vessel wall, which have been shown to promote macrophage activation and the production of proinflammatory cytokines.[200] Although theoretically appealing, the practical use of sevelamer hydrochloride as an effective treatment for chronic inflammation in CKD is questionable, based on the negative outcomes of a recently published clinical trial comparing sevelamer hydrochloride to calcium-based phosphate binders.[201]

F. Heparin

Heparin is a glycosaminoglycan that has seen widespread use as an anticoagulant agent. It has been recognized recently that heparin also possesses antiinflammatory properties, which appear to be distinct from its anticoagulant activity.[202] Such effects were seen in patients with RA,[203] asthma,[204] and ulcerative colitis.[205] A potential mechanism of action is inhibition of leukocyte extravasation through binding to the β2 integrin CD11b/CD18.[206,207] An intriguing possibility is the development of new agents that retain the antiinflammatory properties of heparin, but without the anticoagulant effects.[202,207] How this will affect patients with CKD is yet unclear. The practical impact of a heparin-related antiinflammatory effect in this patient population is questionable, given that heparin is already routinely applied as an anticoagulant with hemodialysis, yet chronic inflammation remains very common in these patients.

G. Megestrol Acetate

Megestrol acetate is a synthetic derivate of progesterone that is primarily used as an appetite stimulant, but it was also found to inhibit the activity of proinflammatory cytokine such as IL-1, IL-6, and TNF-α.[208–212] As an appetite stimulant in HD patients, megestrol acetate was found to improve appetite, increase energy and protein intake, increase dry weight, and improve quality of life.[213–215] The downside is that it can induce many side effects such as headaches, dizziness, confusion, diarrhea, hyperglycemia, thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hypertension, adrenal suppression, and adrenal insufficiency.[208] Large, randomized, controlled trials will be needed to determine if the use of this agent in HD patients can be beneficial for the treatment of chronic inflammation.

H. Bardoxolone Methyl (RTA 402)

Bardoxolone is an antioxidant inflammation modulator in clinical development for inflammation and cancer-related indications. It inhibits immune-mediated inflammation by restoring redox homeostasis in inflamed tissues through the induction of the cytoprotective transcription factor Nrf2 and suppresses the activities of the prooxidant and proinflammatory transcription factors NF-κB and the signal transducers and activators of transcription. In vivo, bardoxolone has shown significant antiinflammatory activity in

various animal models of inflammation such as renal damage in the cisplatin model and ischemia-reperfusion model of acute renal injury. This agent is currently undergoing phase II clinical trials to assess its ability to slow progression of kidney disease in patients with advanced diabetic nephropathy (www.clinicaltrials.gov, identifier: NCT 00811889).

CONCLUSION

Chronic inflammation is very common in patients with CKD and ESRD. The high burden of cardiovascular disease in this patient population and the failure of several traditional therapeutic interventions have lead to an increased focus on the role of nontraditional risk factors, of which chronic inflammation appears to be particularly important. Because several of the causes of chronic inflammation in CKD are not modifiable, pharmacological interventions aimed at lowering inflammation may be promising new alternative strategies used to improve the outcomes in this patient population. Most of the currently available antiinflammatory agents have not been examined in patients with CKD, but some of them have shown effectiveness in reducing the levels of inflammatory markers. These preliminary benefits could translate into improved clinical outcomes, but clinical trials will be needed to prove their efficacy and the safety.

A full list of references are available at www.expertconsult.com.

Chapter 14

SLEEP DISORDERS IN CHRONIC KIDNEY DISEASE

Maria-Eleni Roumelioti, M.D., Patrick J. Strollo, Jr., M.D., FCCP, FAASM and Mark Unruh, M.D., M.Sc.

In the general population, sleep studies using polysomnography show a substantial prevalence of sleep disordered breathing and other causes of sleep fragmentation in healthy adults that clearly contribute to sleepiness and fatigue, hypertension, and cardiovascular disease. Potentially, such sleep disorders could contribute to the very high rates of morbidity and mortality in the chronic kidney disease (CKD) population and to the symptoms of sleepiness and fatigue associated with uremia. Poor sleep and fatigue are commonly encountered complaints by nephrologists caring for patients with CKD (Table 14-1). Although CKD (stages 1-5) is much more prevalent than end-stage renal disease (ESRD), most of the epidemiology of sleep disorders has been performed among those undergoing hemodialysis (HD).

Up to 80% of dialysis patients report sleep problems, which is over twice the rate in the general population, with those undergoing conventional hemodialysis (CHD) showing a high rate of sleep apnea, insomnia, restless legs syndrome, and excessive daytime sleepiness.[1–4] Poor sleep quality and sleep disorders in patients with ESRD are accompanied by a frequent use of hypnotics and diminished quality of life. Both sleep disorders and poor sleep quality lead to daytime symptoms of sleepiness and fatigue, which are frequent and bothersome problems for the chronic dialysis population.[5–8] One hundred prevalent CHD patients were surveyed regarding their willingness to perform more frequent HD; an increase in energy level (94%) and improvement in sleep (57%) were the most commonly cited potential benefits that would justify more frequent HD. However, only 19% of the patients would undergo more frequent dialysis for an increase in survival of 3 years or less.[9]

In this chapter, we will outline the influence of sleep disordered breathing on the kidney. After examining the role of sleep on the kidney, we will characterize the extent to which sleep disorders are found among patients with CKD and ESRD and among patients who have received a kidney transplant. Although many more patients have CKD and are not on dialysis, most studies have examined the extent to which sleep disorders are found among those on dialysis.

POOR SLEEP QUALITY IN ESRD

Several studies of patients on maintenance dialysis have found that 80% of patients with ESRD report some sleep disorder or daytime somnolence.[10–12] There are significant differences between dialysis patients and control subjects in categories of somnolence and in the initiation, maintenance, adequacy, and quantity of sleep.[11] Furthermore, the clinical importance and urgency of this difference in subjective sleep quality is further evidenced by a 31% prevalence of sleep-promoting medication use among dialysis patients.[11] The increased use of hypnotics[13] to treat sleep complaints has an economic cost and exposes the CHD population to medication side effects. In addition, the health burden associated with sleep disturbances is significant, and studies on self-reported sleep problems have strongly been linked to disability days due to

TABLE 14-1 Prevalence of Sleep Problems in Chronic Kidney Disease

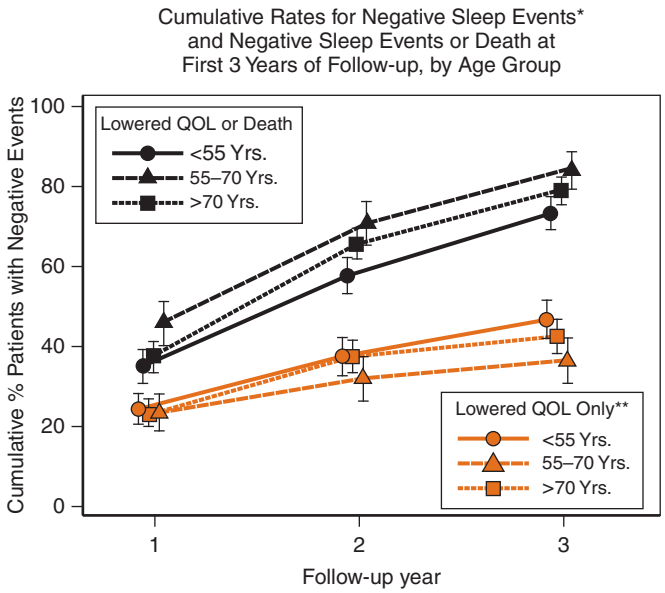
	CHRONIC KIDNEY DISEASE	HEMODIALYSIS	PERITONEAL DIALYSIS	KIDNEY TRANSPLANTATION
Insomnia	-	45%-70%	-	8%-18%
Obstructive Sleep Apnea	2.5%-29%	23%-80%	21%-50%	30%
Restless Legs Syndrome	6%	6.6%-83%	-	4.8%-37%

reduced functional capabilities, greater health care use,[14] and diminished quality of life of dialysis patients.[15,16] Furthermore, among incident dialysis patients, those with poor sleep quality were more likely to report poor physical and mental well-being, decreased vitality, and more bodily pain, whereas those with a clinically significant decline in self-reported sleep quality had a higher risk of mortality.[17] Such a high risk of mortality may reflect acquired sleep disorders, the impact of sleep problems on mood, or the underused treatment of sleep disorders in this population. Previous work has clearly demonstrated that sleep quality can be reliably measured and is clinically meaningful for patients receiving dialysis.

The HEMO study, a multicenter prospective randomized study, examined the effects of hemodialysis dose (Kt/V 1.45 vs. 1.05) and hemodialyzer flux (high vs. low) on patient morbidity and mortality. In the HEMO study, there was neither a survival benefit[18] nor a substantial health-related quality of life (HRQOL)[19] benefit of either high dose of delivered dialysis or high flux. The HEMO Study measured HRQOL using the Kidney Disease Quality of Life-Long Form (KDQOL-LF). In the KDQOL-LF, sleep quality was assessed using 10 items that have a Cronbach alpha of greater than 0.7. In the HEMO study, sleep quality tended to decline more slowly in the high dose compared to the standard dose of dialysis group, with an average difference between dose groups over the first, second, and third year of 1.81 ± 0.95 ($p = 0.06$). For high flux HD the mean of the sleep quality scale was higher in the high flux group by 0.56 points for the first year, 2.95 points for the second year, and 3.26 points for the third year. The mean difference in sleep quality between the flux groups over the 3 years was 2.25 ± 0.95 ($p = 0.02$). The differences in sleep quality by high dose and high flux had small effects and did not meet the Bonferroni criterion for multiple comparisons.[20] Changes in sleep quality over time were examined using clinically significant changes, as defined by a decline in sleep quality by at least 0.5 of the baseline standard deviation.

As shown in Figure 14-1, there was a marked decline in sleep quality across all age groups, and the cumulative rate for a clinically significant decline in sleep quality or death was up to 70% for those over 70-years-old undergoing CHD over the 3 years of the study. The findings of the HEMO study reveal the limits of thrice-weekly in center HD treatments and support the position that poor sleep remains an important public health problem for those undergoing CHD.

Aspects of subjective sleep quality may actually improve after kidney transplantation. In a study by Laupacis and colleagues, 168 patients were followed with a HD questionnaire, a transplant questionnaire, and the Sickness Impact Profile (SIP). The SIP subscale of sleep and rest, which largely measures daytime alertness, was low among patients with ESRD. After the first month posttransplant, the SIP subscale score improved substantially, and remained



* Negative Sleep Event = 11.3 pclnl drop from baseline level (½ SD of baseline values),
** For comparison the 'Lowered QOL Only' statistics included the same number of patients for 'Lowered QOL or Death'. Thus patients who died prior to an annual visit were treated as having experienced no negative QOL events during subsequent follow-up.

FIGURE 14-1 Composite outcome of decline in sleep quality or death and outcome of decline in sleep quality according to group. The 3-year event rate of decline in sleep quality was 46.3% for subjects younger than 55 (< 55 vs > 70; P < .008), 42.1% for those aged 55 to 70 (55 - 70 vs >70; P .08), and 36.0% for those aged 70 and older. The 3-year composite event rate of decline in sleep quality or death was 72.9% for subjects younger than 55 (< 55 vs > 70; P .008), 78.5% for those aged 55 to 70 (55 - 70 vs > 70; P .09) and 83.5% for those aged 70 and older. (M.L. Unruh, A.B. Newman, B. Larive, et al., The influence of age on changes in health-related quality of life over three years in a cohort undergoing hemodialysis, J. Am. Geriatr Soc. 56(9) [2008] 1608-1617.)

improved throughout the 2 years of follow-up. Although the causes of sleep disturbances in the dialysis population are multifactorial and incompletely understood, the detection and treatment of poor sleep in these patients may have a significantly positive impact on clinical outcomes.

EXCESSIVE DAYTIME SLEEPINESS IN ESRD

Excessive daytime sleepiness reflects increased sleep tendency and is an important domain of sleep to measure in patients changing from CHD to nocturnal hemodialysis (NHD). Furthermore, excessive, daytime sleepiness has been associated with most sleep disorders, with hazardous driving and a more limited social role, and it may contribute to the poor vocational and rehabilitation potential that is traditionally associated with ESRD.[21] The diagnosis of excessive daytime sleepiness can be made by self-reporting questionnaires or by objective measures. Subjective assessments using standardized

questionnaires have demonstrated a prevalence of daytime sleepiness of 52% to 67% among patients with ESRD.[12,22]

In addition to subjective assessments, the multiple sleep latency test is an objective measure of daytime somnolence.[23] The multiple sleep latency test is typically performed following polysomnography where a patient is asked to take five naps throughout the day. Using multiple sleep latency testing, excessive daytime sleepiness has been demonstrated in ESRD patients with or without sleep disorders.[24] Stepanski and colleagues assessed sleep in 18 patients undergoing continuous ambulatory peritoneal dialysis (CAPD).[22] In this sample, the average multiple sleep latency test was 6.3 minutes, and there was no association of multiple sleep latency test scores with the presence of periodic limb movements.[22] Hanly and colleagues studied 24 unselected CHD patients. Of the study cohort, 15 patients were subsequently trained on NHD. This group of investigators did not find a significant improvement in daytime sleepiness after conversion to NHD in the short-term.

The use of the multiple sleep latency test has been criticized for being unresponsive to established therapies like positive airway pressure for sleep apnea[25] and for having little relevance to patient's daytime experiences. The American Academy of Sleep Medicine has recommended that the multiple sleep latency test should not be routinely indicated for evaluation of sleepiness in medical and neurological disorders (other than narcolepsy), insomnia, or circadian rhythm disorders.[26] In patients with CKD, it would be reasonable to assess for symptoms of daytime sleepiness in patients and to consider referring patients with high-risk vocations to sleep medicine practices.

INSOMNIA IN ESRD

Insomnia is another sleep disorder commonly encountered among patients with ESRD, and it is defined as a difficulty falling asleep, maintaining sleep, or waking up early in the morning with associated daytime difficulties. Three out of four dialysis patients experience insomnia.[1] The possible connection between insomnia and restless legs syndrome in this population has not been investigated. There is also a lack of trials on insomnia treatments for patients undergoing dialysis. However, one general approach could be: 1) to optimize sleep hygiene, 2) to screen for other sleep disorders, 3) to use a brief trial of cognitive behavioral therapy and hypnotics, and 4) to consider polysomnography in patients who remain symptomatic. For those undergoing HD, it may be reasonable to move the patient to an earlier shift in the day, to consider thermoneutral (cool) HD, and to ask the patient to avoid napping during treatments. Those using overnight peritoneal dialysis (PD) may need to adapt their regimens to avoid frequent alarms and the sensation of abdominal discomfort. There has been a number of studies suggesting that the timing of HD treatments may impact cardiovascular risk and survival.[27–29] Parker and colleagues have shown that sleep propensity increases during CHD treatments, an effect they suggest may be related to treatment induced alterations in arousal and thermoregulatory processes.[30] Overnight dialysis may change daytime experience by having positive effects on sleep and uremia and by freeing up daytime for rest and activity.

SLEEP APNEA IN CHRONIC KIDNEY DISEASE; CONSEQUENCES AND EVALUATION

It is well-known that sleep apnea is a major sleep disorder that leads to repetitive episodes of hypoxemia, hypercapnia, sleep disruption, and activation of the sympathetic nervous system. Physiologically sleep apnea can be obstructive, in which airflow ceases or is substantially reduced despite persistent ventilatory efforts reflecting the presence of upper airway obstruction; central apnea, in which airflow is absent due to cessation of ventilatory efforts; and mixed apnea, reflecting both central and obstructive patterns within an event. The most common metric for sleep apnea is the apnea-hypopnea index, which is the number of apneas and hypopneas in 1 hour of sleep.[31] There are several different criteria for the apnea-hypopnea index including the Chicago Criteria[32] and the Centers for Medicare and Medicaid Services (CMS) criteria.[33] The CMS criteria have been used clinically and were based, in part, on findings from the Wisconsin Sleep Cohort and the Sleep Heart Health Study.[33] Using the CMS criteria, apnea has been defined as a cessation of airflow for at least 10 seconds. Hypopnea has been defined as an abnormal respiratory event lasting at least 10 seconds with an at least 30% reduction in airflow as compared to baseline and is associated with at least 4% oxyhemoglobin desaturation. Figure 14-2 demonstrates the pattern of severe obstructive sleep apnea hypopnea syndrome observed by polysomnography in a thin, old, male HD patient.

Sleep apnea causes gas exchange abnormalities, sleep fragmentation, and autonomic activation, which have all been implicated as causes of substantial adverse health events.[34,35] This sleep disorder commonly produces daytime sleepiness,[36] decreased quality of life,[37] and impaired cognitive ability.[38] Sleep apnea is also an independent risk factor for hypertension[39] and is associated with cardiovascular disease including stroke, myocardial infarction, and congestive heart failure after adjustment for obesity and other potential confounders.[40,41] In the general population, the treatment of sleep apnea with continuous positive airway pressure (CPAP) improves blood pressure,[42] daytime symptoms, and quality of life.[43]

The risk factors for sleep apnea in CKD have to be extrapolated from the general population and the main reason for this is that only small sample size studies have been conducted in this high-risk population. Table 14-2 outlines factors possibly related to sleep apnea in the CKD population, like demographic factors, health behaviors, physical exam findings, symptoms, and comorbidities. Older adults and men have a significantly higher likelihood of sleep apnea. In a physical exam, patients with a thick neck, obesity, a full upper airway, and high blood pressure are more likely to suffer from obstructive sleep apnea. Patients that use tobacco and alcohol and those that are thought to snore are also at higher risk of sleep apnea. Lastly, patients with symptoms of sleepiness and fatigue and those with a diagnosis of hypertension or diabetes may have sleep apnea. Therefore, symptoms of sleepiness and fatigue may be very helpful in discerning which patients with CKD need a diagnostic study for sleep apnea.

The gold standard for the diagnosis of sleep apnea is overnight in-laboratory polysomnography, including electroculogram, electroencephalogram, electromyogram, respiratory airflow, oxygen saturation, reparatory effort bands, electrocardiogram, body position, and video. Patients are observed

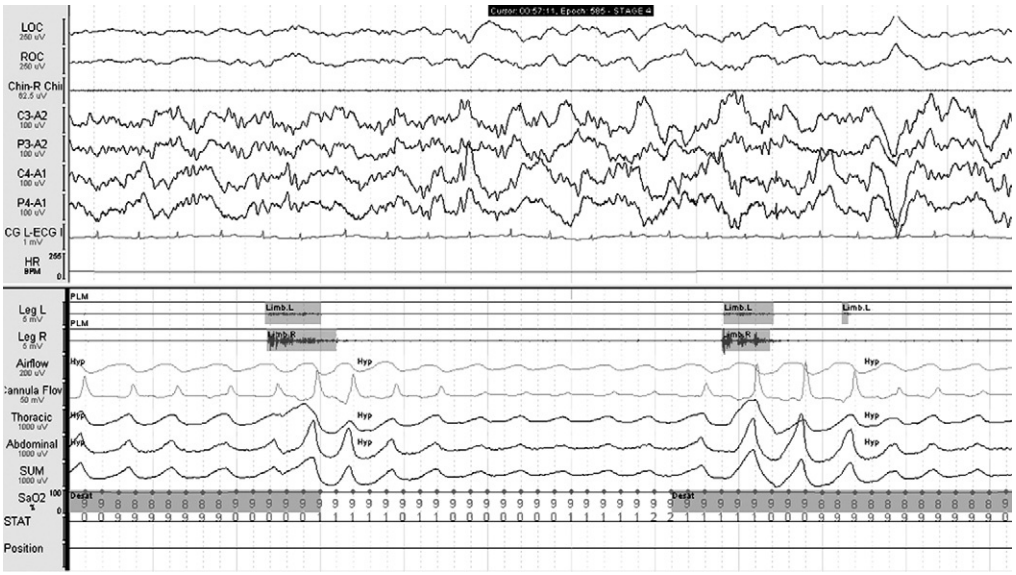


FIGURE 14-2 Polysomnography of a hemodialysis patient with severe obstructive sleep apnea. The thoracic and abdominal bands are diminished but in phase without obvious desaturation. The total number of apneas and hypopneas with greater than or equal to 3% desaturation per hour of sleep was 82.7. Lowest oxyhemoglobin saturation during sleep was 74%.

TABLE 14-2 Risk Factors for Sleep Apnea in the Chronic Kidney Disease Population

GENERAL
Older age
Male gender
Family history
Excessive daytime sleepiness (when wakefulness is required)
History of (car) accidents due to excessive somnolence
Habitual snoring
Sleep apnea or excessive respiratory effort during sleep (noticed by another person)
Tobacco use
Alcohol abuse
Chronic therapy with sedative drugs and/or pain medications
Anatomical abnormalities of the upper airways: macroglossia, tonsillar hypertrophy, short mandible, large neck size
Obesity
Severe hypertension
Congestive heart failure
Diabetes mellitus
Metabolic syndrome
KIDNEY DYSFUNCTION–RELATED
Volume overload

overnight by a technician who monitors signal quality and adjusts sensors if there is a positioning issue. Despite the effort at optimizing polysomnography signals, in-laboratory studies suffer from night-to-night variation, scoring variation among centers and technicians, and a high burden to the participants.

Over the past 2 decades, the measurement of sleep apnea has moved from the sleep laboratory to the home setting. Beginning in the 1990s, ambulatory polysomnography was used to measure the severity of sleep apnea while avoiding the need for the study participant to travel to a sleep laboratory.[44–46] The cost of in-home polysomnography is high, because the sleep technicians at multiple sites need to be trained and certified. Although in-home polysomnography has a smaller burden for the participant, the limitations of in-home polysomnography are similar to in-center polysomnography, with night-to-night variability and scoring variability among centers. The alternatives to a full polysomnography include single channel oximetry and cardiopulmonary studies with more novel devices, which use miniaturized electronics and multiple channels to provide an accurate measure of sleep apnea. Because sleep staging is not thought to be necessary for measuring the severity of sleep apnea, the Institute of Medicine report called for further use of portable monitors to measure sleep apnea.[47]

SLEEP APNEA, HORMONES, AND PROTEINURIA

Previous studies have noticed some changes in the urinary volume and urinary electrolytes among patients with obstructive sleep apnea-hypopnea. In a study by Krieger and colleagues, patients with obstructive sleep apnea-hypopnea and with presumably normal renal function had a significantly higher fractional sodium and chloride urinary excretion than did those without obstructive sleep apnea-hypopnea. Notably, the fractional sodium and chloride urinary excretion decreased toward control levels in these patients after initiation of nasal CPAP treatment, which effectively treated the obstructive sleep apnea-hypopnea.[48]

Why and how does obstructive sleep apnea-hypopnea alter urinary volume and electrolytes? Elevated levels of atrial natriuretic peptide among patients with obstructive sleep apnea-hypopnea have been demonstrated.[49] Furthermore, sleep apnea may also mediate changes in salt and water metabolism by modifying other hormones such as brain natriuretic peptide (BNP), angiotensinogen II, aldosterone, and arginine vasopressin. However, studies of patients with sleep apnea have led to conflicting findings, with some studies reporting higher levels and other studies reporting normal levels of both atrial

natriuretic peptide (ANP) and BNP. Additionally, some studies have shown that sleep apnea increases sympathetic tone and angiotensin II production. Angiotensin II in turn increases aldosterone production in the adrenal gland, and the use of CPAP has been shown to reduce aldosterone levels and improve blood pressure.[50] However, other studies have demonstrated increases in aldosterone levels.[51] It is important to notice that the angiotensin and aldosterone levels are cyclic, and they depend on volume status and body position. Thus, it could be that conflicting findings from the literature depend on the specific timing of hormone levels measurement.

Obstructive sleep apnea-hypopnea has also been associated with resistant hypertension in a number of small studies. Furthermore, among patients with resistant hypertension, sleep apnea severity has been associated with aldosterone levels. Calhoun and colleagues, using a questionnaire, demonstrated an association of risk for sleep apnea with higher plasma aldosterone levels.[52] This group subsequently demonstrated an association of morning plasma aldosterone concentration with sleep apnea severity measured by polysomnography in hypertensive patients.[53] This work suggests that one could consider either treating obstructive sleep apnea-hypopnea or use mineralocorticoid receptor antagonists to lessen the severity of obstructive sleep apnea-hypopnea in patients with resistant hypertension.

The contribution of obstructive sleep apnea-hypopnea to proteinuria in both patients with diabetes and without diabetes remains unclear due to the small effect and due to the confounding role of obesity and hypertension. Early studies demonstrated an association of obstructive sleep apnea-hypopnea with proteinuria among obese patients,[54] with a decrease in proteinuria when apnea was treated.[55] More recent cross-sectional studies of the nondiabetic sleep apnea population have failed to demonstrate this association.[56,57] However, a study compared 62 untreated hypertensive patients with obstructive sleep apnea-hypopnea to 70 untreated hypertensive patients without obstructive sleep apnea-hypopnea and demonstrated that obstructive sleep apnea-hypopnea patients had increased albumin-to-creatinine ratio after accounting for differences between the two groups.[58] In a study of 496 adults with overnight polysomnography and overnight 8-hour urine collection, there was a significant association between the apnea-hypopnea index severity and albumin-to-creatinine ratio.[59] In this report, those with apnea-hypopnea index greater than 30 were more likely to suffer from obesity, hypertension, diabetes, and older age suggesting that these variables could also be contributing to these findings.[59] The absolute difference in albumin-creatinine ratios was significant, but small in magnitude.

PREVALENCE OF SLEEP APNEA IN CHRONIC KIDNEY DISEASE

Sleep apnea is thought to be more prevalent among patients with CKD compared to the general population. A comparison of CKD and dialysis patients demonstrated that HD subjects had less rapid eye movement sleep, more brief arousals, and a trend toward more severe sleep apnea.[60] Another study of 35 patients with CKD (mean creatinine clearance 27 ml/min/1.73 m^2) demonstrated that 50% of the CKD population had mild sleep apnea and approximately one third had moderate sleep apnea.[61] A large study of community-dwelling men has examined the association of kidney function with sleep apnea.[62,63] These findings suggest that age and body mass index were important modifiers. In addition, the extent of the relationship between sleep apnea and kidney function was dependent on how kidney function was estimated. The authors demonstrated an association between sleep apnea and cystatin-C that was attenuated by adjustment for body mass index. In a registry study from Japan, there was also an association between sleep apnea diagnosed in a sleep center and CKD compared to the prevalence CKD in the population estimated from a large screening study.[64] A large cross-sectional study of patients in the United States from a health care plan demonstrated an association of an estimated glomerular filtration rate less than 45 ml/min/1.73 m^2 with sleep apnea diagnosis using ICD-9 coding for sleep apnea and CPT coding for positive airway pressure devices.[65] However, the overall rate of sleep apnea was low in this population, and there did not appear to be a dose–response relationship between the level of kidney dysfunction and the severity of sleep apnea. It is hard to interpret studies of prevalence based on billing records because this would misclassify an underrecognized disorder.

SLEEP APNEA IN ESRD

Severe sleep apnea has a much higher prevalence among those on dialysis than in the general population. The prevalence of sleep apnea in the middle-aged, general population has been reported to be 2% to 4%.[66] In contrast, studies in the dialysis population using survey questionnaires, partial channel polysomnography, or overnight polysomnography have demonstrated a prevalence rate of greater than 50% in CHD patients.[22,67–69] However, these studies may be biased by differences in comorbid conditions such as cardiovascular disease, diabetes mellitus, and obesity together with a referral bias. The prevalence of severe sleep apnea among a community-based sample of CHD patients was found fourfold higher than a comparison group matched for age, gender, race, and body mass index (BMI).[70]

Despite the apparent prevalence of sleep apnea in ESRD, the etiology remains unknown. In a community-based study, the independent risk factors for sleep apnea were male gender, age, BMI, neck girth repeated breathing pause frequency and snoring.[71] However, these risk factors have not been associated with sleep apnea among patients with ESRD. As in heart failure, ESRD may cause central destabilization of ventilatory control and upper airway occlusion. Other causes that have been suggested include anemia, upper airway uremic myopathy, neuropathy, uremic toxins, cytokines, increased extra cellular fluid volume leading to narrowed upper airway, and leptin resistance.[69,72]

Interestingly, NHD partially corrects sleep apnea.[73] A study examined 14 patients who where undergoing CHD and were subsequently switched over to NHD. The patients underwent polysomnography before and after they switched modes of dialysis. A marked reduction in sleep apnea among seven patients was demonstrated as shown in Figure 14-3;[73] however, these NHD patients continued to have frequent arousals from sleep, diminished sleep time, diminished rapid eye movement sleep time, and diminished sleep efficiency. Although some episodes of apnea-hypopnea were diminished, the study could not demonstrate a possible etiology, and its findings also

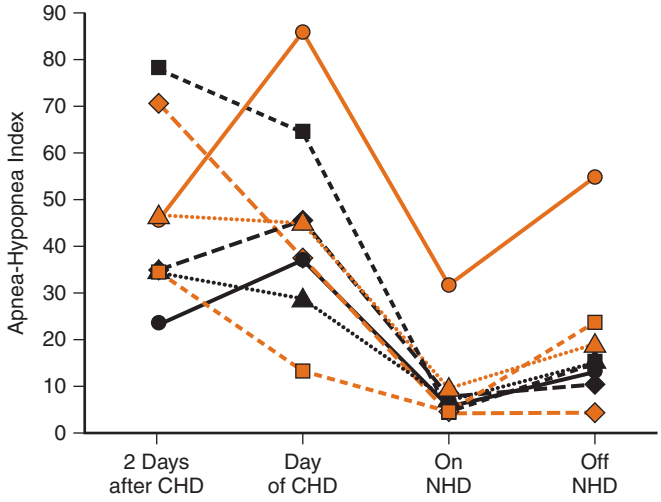


FIGURE 14-3 Change in sleep apnea-hypopnea index in seven patients with nocturnal hemodialysis. CHD denotes conventional hemodialysis, and NHD nocturnal hemodialysis. The mean values are represented by the *broken black line*. Data from the single patient who had Cheyne-Stokes respiration during conventional hemodialysis and persistent obstructive sleep apnea during nocturnal hemodialysis are represented by the *solid black line*. (From P.J. Hanly, A. Pierratos, Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis, N. Engl. J. Med. 344 [2001] 102–107.)

suggested that overall sleep architecture did not improve with intensive NHD.[73] This underlines the importance of assessing a full spectrum of sleep outcomes.

The contribution of uremia and volume overload to the pathogenesis of sleep apnea in ESRD has also been supported by the improvement in sleep apnea with use of a nocturnal automated peritoneal cycler. In a small study performed at two PD centers in Hong Kong, Tang and colleagues have demonstrated a reduction in the severity of sleep apnea with the use of nocturnal cycler-assisted peritoneal dialysis.[74] In 46 patients that transitioned from nocturnal peritoneal dialysis (NPD) to continuous ambulatory peritoneal dialysis (CAPD), the apnea-hypopnea ratio increased from 3.4 ± 1.3 to 14.0 ± 3.5 during CAPD ($p < 0.001$). Of note, the CAPD patients demonstrated a marked increase in weight (2.7 kg) and no change in pulmonary function. These findings suggest that a component of sleep apnea among PD patients in this study may be due to differences in fluid removal between modalities as performed by these two centers. As demonstrated in Figure 14-4, this hypothesis was further examined using magnetic resonance imaging of the upper airway, which demonstrated a reduction in cross-sectional space in the upper airway among 14 patients who transitioned from NPD to CAPD.

Sleep apnea contributes to the substantial morbidity and mortality of the CHD population. Sleep apnea leads to the poor daytime experiences of those on dialysis[67] by causing excessive daytime sleepiness and diminished quality of life.[4,75] Sleep apnea has also been associated with an increased risk of cardiovascular disease in ESRD[76,77] and a disruption in normal non–rapid eye movement sleep by attenuating the parasympathetic ("vagal") modulation of heart rate. Increased cardiac and peripheral adrenergic drive may help explain why sleep apnea and nocturnal hypoxemia have been associated with left ventricular hypertrophy,[78] arterial hypertension,[79] and increased cardiovascular events

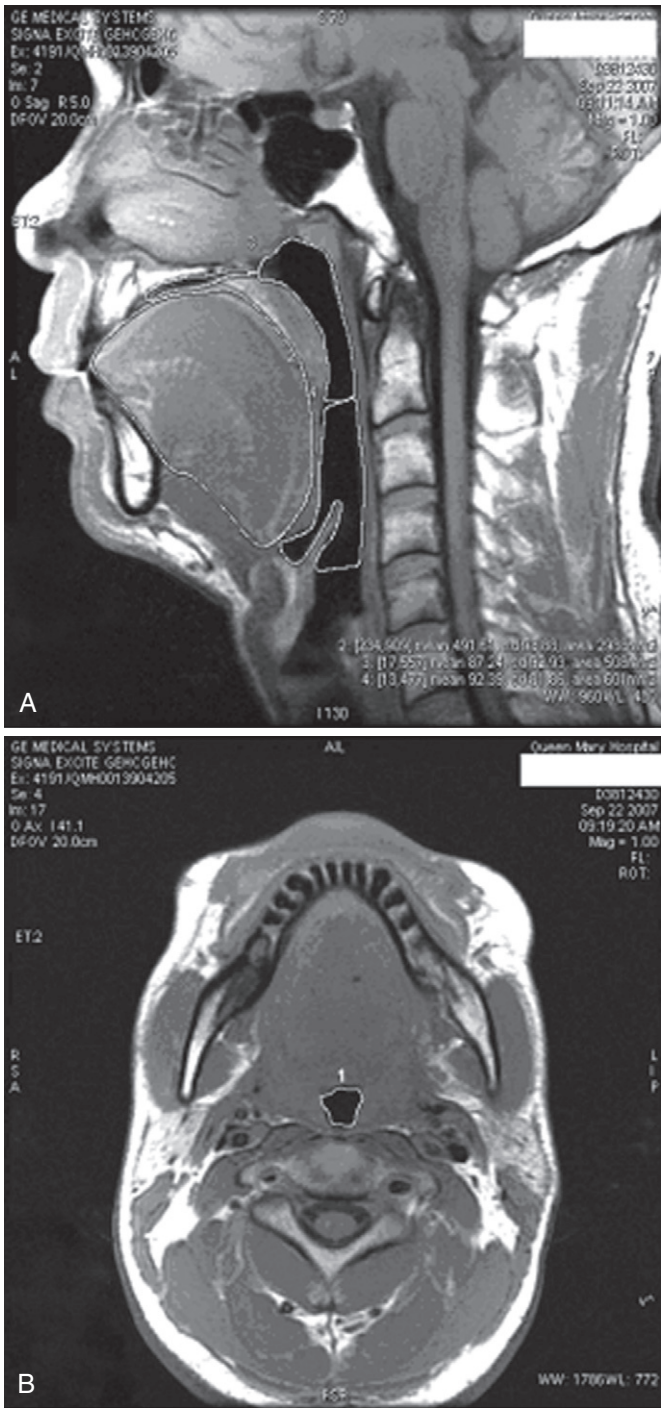


FIGURE 14-4 **A,** Anatomical demarcations of the predefined landmarks (see text for definition) of the upper airway illustrated by magnetic resonance imaging. Representative sagittal image showing the anatomical boundaries for measuring the areas of the oropharynx, (1) tongue, (2) nasopharynx, (3) and hypopharynx. (4) The corresponding volumes were then calculated on the basis of the sagittal areas of a series of contiguous slices and on the thickness of the scan slices. **B,** Representative axial image showing the slice at which the pharyngeal area was the smallest[1] among contiguous axial slices of the pharynx. (S.C. Tang, B. Lam, A.S. Lai, et al., Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance, Clin. J. Am. Soc. Nephrology. 4(2) [2009] 410-418.)

in the CHD population.[77] In addition to the neurohormonal effects of sleep apnea, Jung and colleagues studied 26 CHD patients and demonstrated an association between apnea-hypopnea index and coronary calcification scores.[80] The authors propose that nocturnal hypoxemia followed by reoxygenation may lead to free radical generation, thus facilitating the process of coronary calcification.

SLEEP APNEA IN KIDNEY TRANSPLANTATION

Similar to the results of NHD, improved clearance of uremic toxins after successful renal transplantation would be expected to alleviate sleep apnea. However, the data on sleep apnea in kidney transplantation are scant. With the exception of two case reports describing reversal of sleep disordered breathing after transplantation and a recent study of patients with mild sleep apnea, other studies have failed to show significant benefit. Several case reports suggest the reversal of this sleep disorder with kidney transplantation. Indeed, two patients with ESRD were reported to have severe sleep apnea with an apnea-hypopnea index of 50 and 80, respectively that improved to 5 and 9, respectively.[81] Another individual with ESRD and severe sleep apnea was reported to improve, but in this case, the investigators were unable to administer a follow-up polysomnography and were left with demonstrating fewer nighttime oxyhemoglobin desaturation episodes.[72] The problem with these case reports is that only those that reported markedly improved sleep apnea were studied. In addition, the types of apnea-hypopnea episodes were not reported. A recent prospective study of nine HD patients with mild sleep apnea demonstrated improvement in apnea-hypopnea index among eight of the nine patients after kidney transplantation.[82] Beecroft and colleagues reported that kidney transplantation was associated with a significant reduction in blood urea nitrogen and serum creatinine without significant changes in apnea-hypopnea index[83] and found no significant correlation of "responders" (significant improvement) with BMI and comorbid conditions. However, the role of steroids and immunosuppressive protocol was not investigated. Sleep apnea may contribute to the high prevalence of sleep-related complaints in this patient population.[62–64] Because cardiovascular disease remains the leading cause of mortality in renal transplant patients[65] and sleep complaints are prevalent in transplant patients, further research is required to determine the extent to which kidney transplantation may improve sleep apnea.

TREATMENT OF SLEEP APNEA AMONG PATIENTS WITH ESRD

In the ESRD population, CPAP was used in a very preliminary study on eight patients with some improvement in nocturnal oxygenation.[84] It is interesting that CPAP is not widely used among patients with ESRD because only 2% have the diagnosis according to the United States Renal Data System (USRDS). The association of sleep apnea with uremia led some investigators to examine the impact of dialysis on sleep apnea. In a case report, a single patient presenting with uremia had a marked improvement of sleep apnea by treatment with HD therapy.[85] The number of recorded apneas decreased from 108 to eight, and the lowest oxyhemoglobin saturation improved from 78% to 86%. This report is limited to the experience of a single patient. In addition, the delivered dose of dialysis and blood gas changes was not reported. The impact of the dialysate on sleep apnea among those undergoing HD has been examined. Using a crossover design, it was demonstrated that acetate dialysate was associated with central apneas in HD patients.[86] Ten patients, 8 males and 2 females, aged 35 to 71 years, with a dry weight of 55 to 72 kg, who were on CHD 15 hours per week for 6 to 67 months were randomly assigned first to acetate or bicarbonate and then to the other type of buffer. After a series of six sessions using the same buffer, polysomnographic recordings from 9:00 PM to 6:00 AM were obtained. Age, gender, weight, data of first dialysis session, blood pressure, and sleep disorder-related symptoms were not correlated with the sleep apnea syndrome. Prolonged or important oxyhemoglobin desaturations were never observed. Central apnea occurred more frequently during the night following acetate dialysis: $x = 33$ (0-180) versus 3, (0-15) $p < 0.05$. Obstructive apneas were not different. A defective modulation of ventilatory control after HD with acetate might be held responsible for the central apnea, which would constitute one more reason supporting the use of bicarbonate buffers in HD. Acetate is no longer widely used for HD treatments.

The effects of normalizing hematocrit on sleep disorders, sleep patterns, and daytime ability to remain awake were examined in ESRD patients. Ten HD patients who were on recombinant human erythropoietin therapy and who had sleep complaints were studied by polysomnography. The study was conducted in two subsequent time points, once while patients were moderately anemic (mean hematocrit, 32.3%) and again when hematocrit was normalized (mean hematocrit, 42.3%) by increased erythropoietin dosing. All subjects experienced highly statistically significant reductions in the total number of periodic limb movements causing arousals ($p = 0.002$). Nine of 10 subjects showed reductions in both the arousing periodic limb movements index ($p < 0.01$) and the overall periodic limb movements index ($P = 0.03$) after the hematocrit was normalized, while measures of sleep quality showed trends toward improvement. In the same study the Maintenance of Wakefulness Test demonstrated significant improvement in the length of time patients were able to remain awake (9.7 versus 17.1 minutes; $P = 0.04$).

High flux HD was associated with a lower number of apneic-hypopneic episodes[87] among those participating in an ancillary to the HEMO study. The limitations of this ancillary study were that not all patients were recruited, patients were examined as treated, and no baseline studies were performed. The number of patients randomized was insufficient to guarantee an equal distribution of factors across the study arms. However, this study offers preliminary evidence that the type of HD membrane may influence sleep disordered breathing.

RESTLESS LEGS SYNDROME ASSOCIATED WITH POOR MENTAL HEALTH AND SHORTER SURVIVAL IN ESRD

Restless legs syndrome (RLS) is a sleep disorder commonly reported among persons on HD, but little is known about the prevalence of RLS in the CKD population. RLS is a neurological disorder characterized by paresthesias and dysesthesias that often occur in the evening and are improved

by movement of the affected limb.[88,89] RLS is diagnosed based on the criteria of the International Restless Legs Syndrome Study Group (IRLSSG): 1) an urge to move, usually due to uncomfortable sensations; 2) motor restlessness; 3) worsening of symptoms by relaxation; and 4) symptoms worse in the evening and early in the night.[89] Studies using a gold standard neurologist interview have found that approximately 23% to 33% of patients undergoing CHD report symptoms of RLS.[90,91] In addition, data using a questionnaire based on IRLSSG criteria have also shown a 33% prevalence of RLS among CHD patients.[92]

The risk factors for RLS in those with ESRD remain unclear. In the general population, older age, increasing BMI, diabetes, cigarette smoking, low exercise, and low alcohol consumption have been correlated to restless legs.[93] It may be that patients who are diabetic have small fiber neuropathy that mimics the symptoms of RLS.[94] Older age, higher BMI, gender, work status, education, pregnancy, and alcohol and tobacco use have also been associated with severe RLS symptoms.[93] In the general population, it has been suggested that RLS is caused by blockade of the D_2 receptor in the diencephalon,[95] whereas among dialysis patients inadequate dialysis and secondary hyperparathyroidism may predispose to the syndrome.[91,96]

RLS has been associated with substantial morbidity and mortality in the ESRD population. Both in the general population and the CHD population, restless legs are associated with poor mental health.[93,96,97] Symptoms of restless legs were associated with a lower HRQOL among a nation wide sample of 900 incident dialysis patients.[98] In HD patients, RLS has been associated with shorter survival after adjusting for age, gender, and duration of dialysis session.[96,98]

Several mechanisms may explain the association of RLS with an increased risk of death. It has been demonstrated that RLS and periodic limb movement disorder increase sleep fragmentation, and this fragmented sleep may in turn increase the cardiovascular risk.[99] In a previous study RLS was associated with HD compliance, and it may be that poor adherence to the dialysis prescription in patients with RLS leads to the increased mortality risk.[96] Lastly, it may be that RLS severity is a marker of inadequate dialysis, inflammation, or periodic limb movements. In a retrospective study of 29 selected symptomatic patients, Benz found that periodic limb movements were strongly related to mortality.[100]

Iron has been generally used to treat restless legs syndrome[101] and ferritin has been found to be a useful marker relating RLS to iron deficiency.[102] Studies examining the use of intravenous (IV) iron in the treatment of idiopathic RLS are ongoing. If iron metabolism does affect restless legs, then the mechanism is probably central, because iron is a key catalyst in brain dopamine metabolism, and serum iron levels correlate poorly with central nervous system concentrations.[103–106] However, a study of CHD patients has found that those patients who met clinical criteria for RLS were not more likely to have iron deficiency.[91]

The use of IV iron in the treatment of RLS among ESRD patients has been studied in a small randomized study examining short-term changes in symptoms and adverse effects of IV iron.[107] Hemodialysis patients determined to have RLS by the IRLSSG criteria were administered either 1 g of iron dextran or normal saline IV in a blinded fashion. Eleven patients were randomly assigned to the administration of iron dextran and 14 patients to the administration of normal saline. Iron infusion was associated with a significant, but transient, reduction in symptoms of RLS in patients with ESRD.[107] It would be important to assess the impact of IV iron therapy on sleep quality, quality of life, and survival of this at-risk population.

There is not a particular type of dialysis recommended for patients with RLS. The timing and type of dialysis should be individualized to minimize patients' symptoms of restless legs. For example, patients undergoing HD in the evening with severe symptoms of restless legs may benefit from a change to the morning shift where symptoms of RLS may be less intense than later in the day. Likewise, patients using NPD may be changed to CAPD, which is done predominantly during the day. This change permits PD patients to have more freedom to move in the late evening. Regardless of the type or timing of dialysis treatment, it is important to treat RLS according to the severity of symptoms.

An approach to the treatment of RLS among patients with kidney failure has been recently outlined.[108] Patients with complaints of restless legs syndrome should have a history and physical examination that excludes causes of pain in the extremities such as peripheral vascular disease and neuropathy. The severity of RLS should be clinically assessed, and the clinicians should consider using a validated instrument to document RLS severity. If the patient has mild to moderate RLS, then the team should focus on nonpharmacological interventions (i.e., using a bicycle, distracting activities). If RLS is severe, then it would be important to use a pharmacological intervention to improve quality of life and encourage adherence with dialysis.

There are several characteristics of uremic RLS that should be considered. First, uremia may attenuate the response of RLS to dopamine. In a study of idiopathic RLS and uremic RLS, those with uremic RLS demonstrated a smaller response to dopamine. However, other studies have demonstrated clinically significant effects to dopamine agonists in those undergoing HD. Second, RLS in CKD presents in the milieu of other potential sleep disorders. If there is no improvement in daytime functioning or symptoms with treatment of RLS, it may be reasonable to reassess the patient closely for other chronic health conditions, such as anemia, and to have a low threshold for use of polysomnography because there is a high rate of sleep apnea.

PERIODIC LIMB MOVEMENTS THOUGHT TO BE WIDELY PREVALENT IN PERSONS ON HEMODIALYSIS

Whereas RLS is a syndrome diagnosed using a validated questionnaire based on standard criteria, the diagnosis of periodic limb movements requires the monitoring of leg movements overnight. Periodic limb movements are characterized by periodic episodes of repetitive and highly stereotyped movements. Periodic limb movements are typically dorsiflexions of the foot that last 0.5 to 5 seconds and appear especially during light sleep.[109] For a diagnosis of periodic limb movements, polysomnography recordings are essential. A periodic limb movements index (the number of periodic limb movements in one hour) of greater than five is considered abnormal.[110] Figure 14-5 demonstrates abnormal periodic limb movements measured by polysomnography.

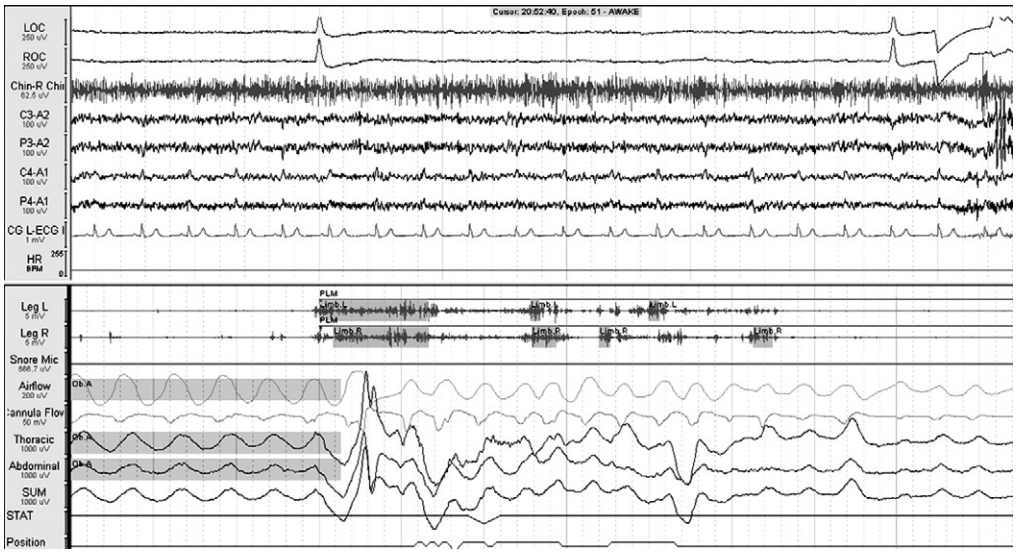


FIGURE 14-5 Polysomnography of a hemodialysis patient with periodic limb movements and restless legs syndrome. This patient had a diagnosis of restless legs and had severe sleep apnea. The total number of apneas and hypopneas per hour with greater than or equal to 3% oxyhemoglobin desaturation per hour of sleep was 38.6. The sequence of leg movements shown here is not typical for periodic limb movement disorder. The periodic limb movement index was 26.4 movements per hour of sleep.

Previous studies have demonstrated that 70% of symptomatic HD patients had a periodic limb movements index greater than 5.[111] Although periodic limb movements have been frequently documented in the general population, the impact of periodic limb movements on sleep has been unclear and controversial. In the study of 10 patients on HD with RLS, there were no significant differences in periodic limb movements or sleep continuity when compared to a group of idiopathic RLS subjects.[112] In the dialysis population, periodic limb movements have been associated with increased sleep tendency and shorter survival in small studies that did not account for comorbidities or RLS.[100,113] In a study that examined both RLS and periodic limb movements in CHD, there was not a substantial difference between those with and without periodic limb movements in the domains of insomnia, daytime sleepiness, depression, and HRQOL.[114]

Periodic limb movements may occur as an isolated condition, or they may be related to medications, neurological disorders, or sleep apnea. Because periodic limb movements and sleep apnea are both common among patients on HD, it is important to distinguish between intrinsic periodic limb movements and secondary periodic limb movements triggered by arousals from sleep apnea episodes. Although the exact origin and pathophysiology of periodic limb movements remain unclear, several studies have suggested a subcortical site of origin.[95] In the general population, periodic limb movements have been associated with diminished cognition and poor attention. In the HD population, a study of 10 subjects demonstrated a significant reduction in the number of periodic limb movements with a normalization of the hematocrit using erythropoietin.[111]

SLEEP IN CHILDREN WITH CHRONIC KIDNEY DISEASE AND ESRD

Pediatric CKD and its consequences are a public health concern, because many children currently being treated for CKD are progressing to ESRD. More attention is being paid to the importance of improving the educational, psychosocial, emotional, and physical health of children and adolescents with CKD, because improvements in therapy have led to an increasing number of children with CKD reaching adulthood. Sleep is vital for maintaining and promoting health and growth in children, and previous work indicates that sleep problems are prevalent among children with other chronic illnesses.

There are many compelling reasons why a better understanding of sleep disorders and symptoms of sleepiness and fatigue should feature prominently in the care of children with CKD. Sleep disturbances can have a deleterious effect on a child's behavior, ability to learn, and physical development. In addition, parenting and other aspects of family function can be seriously affected by disturbed sleep in a child, because children with CKD or ESRD depend on their caregivers for their parenting and medical support. Furthermore, the urgent need to examine sleep and fatigue in the pediatric CKD population is supported by our preliminary work, which demonstrated marked differences in sleep across the lifespan of those with ESRD. Despite having more sleep time and deep sleep, young adults on hemodialysis remain burdened by self-reported sleepiness and fatigue.

While sleep and fatigue symptoms have been widely documented among adults with CKD and ESRD, assessment of sleep and fatigue problems in children with CKD has been limited, with one study demonstrating that 86% of children and young adults with ESRD on dialysis had a sleep problem. Twenty-one children (aged 6 to 20 years) with ESRD and their parents responded to questionnaires that assessed four symptom domains of sleep disorders: 1) sleep-disordered breathing, 2) RLS or periodic limb movements, 3) excessive daytime sleepiness, and 4) inadequate sleep time.[115] Overall, 18 (86%) of the children undergoing dialysis (mean age [SD] 14.2 years, [1.1] gender [M/F] 11/10) endorsed sleep disturbance symptoms. The conclusions of the study were that sleep disturbances are very common and underrecognized in pediatric dialysis patients.[115] Another recent small study

examined RLS among 26 pediatric patients with CKD (stages 1 to 5) demonstrating restless legs in 35% of these patients.[116] There was no significant difference in symptoms of daytime sleepiness between the group with RLS and the group without RLS in this small study.

CONCLUSION

Although patients with CKD or ESRD of all ages show a high prevalence of sleep disorders with severe health and socioeconomic consequences, most cases remain undiagnosed and untreated. The recognition of sleep disorders in this population is often complicated by the presence of comorbid illnesses or the uremic syndrome itself. Proper assessment and adequate therapy of sleep disordered breathing may hold promise to significantly decrease the cardiovascular risk in these patients. More generally, most sleep disorders such as insomnia and RLS are treatable. Therefore, it is essential to have awareness of the diagnosis and therapy of these important conditions, which may lead to a better quality of life, better rehabilitation, and even better survival of this patient population.

A full list of references are available at www.expertconsult.com.

Chapter 15

KIDNEY DISEASE AND MEDICATIONS

Wolfgang C. Winkelmayer, M.D., Sc.D.

WHY FOCUS ON MEDICATIONS IN PATIENTS WITH KIDNEY DISEASE?

Recent data indicate that as many as 13% of the general U.S. population (26 million) have chronic kidney disease (CKD) and that the prevalence of CKD is increasing over time.[1] In addition, more than 530,000 individuals in the United States had end-stage renal disease (ESRD) requiring dialysis or had a functioning kidney transplant at the end of 2007.[2] Relatively little information, however, is available on the use of prescription drugs in patients with kidney disease, including those with CKD not requiring renal replacement therapy, patients on maintenance hemodialysis or peritoneal dialysis, and those with a functioning kidney transplant. On one hand, the limited information available indicates that medication use is generally high in these populations, reflecting the multiple comorbid conditions usually present in patients with kidney disease and the burden of therapies for kidney disease and its complications. On the other hand, however, there is evidence that recommended medications and other treatments are underused in patients with various degrees of kidney disease compared to patients free from kidney disease. The reasons for this paradox are poorly understood. Important aspects include the absence of evidence on the efficacy and safety of most medications in patients with kidney disease. Indeed, patients with CKD, ESRD, and kidney transplants have often been excluded from the efficacy trials that define evidence-based medical practice today. In addition, the relatively few trials that specifically enrolled and were restricted to patients with CKD or ESRD were often negative or inconclusive. Another possible contributing cause of underuse of recommended treatments is the high pill burden in patients with kidney disease. Adherence with prescribed medications is inversely correlated with the number of pills prescribed, so patients may choose to eliminate certain medications from their daily regimen. Patients may prioritize based on economic considerations or on perceived benefit, which may not align with the drugs yielding the greatest benefit from an effectiveness or cost-effectiveness perspective. In addition, providers may experience uncertainty in how to most appropriately prescribe treatment to patients with kidney disease. Several factors need to be considered when selecting medications for treatment in patients with chronic kidney disease: altered drug release and absorption from the gastrointestinal tract, altered drug binding and transport, differences in the metabolic processing of medications and their metabolites, and changes in their excretion, especially in medications that are partially or predominantly excreted by the kidney or those removed by extracorporeal therapies. In addition, polypharmacy naturally leads to an increased risk of drug-drug interactions. This chapter will review these issues in detail and discuss the pertinent literature. Detailed drug dosing recommendations for specific compounds, however, have been covered extensively in the parent book of this series,[3] and this information will not be repeated herein.

ALTERED PHARMACOLOGY OF MEDICATIONS IN KIDNEY DISEASE

The kidney plays a complex and delicate role in the handling of drugs and their metabolites. It has long been known that medications that are predominantly excreted by the kidney need to be dose-adjusted in patients with impaired kidney function. The true impact of reduced kidney function, however, goes way beyond this simple concept, and we continue to discover and appreciate new facets of how uremia alters many other aspects of the pharmacokinetics and pharmacodynamics of several drugs: the rate and extent of drug absorption, distribution among real or virtual spaces, metabolism, and excretion of prodrugs, drugs, and their active or toxic metabolites.

For example, it has been shown that uremia changes the pH in the stomach, leading to a relatively alkalinized milieu, which then affects dissolution of certain drugs, thus leading to reduced absorption.[4,5] Phosphate binders are a good example of pH-dependent effectiveness.[6] In addition, therapeutic ingestion of cationic molecules including resins, such as those used for the binding of inorganic phosphate, can also decrease drug absorption.[5,7] Furthermore, gastrointestinal transit time may be changed in patients with advanced kidney disease and thus may affect drug absorption.[8] Uremia may also alter the effect of the first-pass mechanism in the gut and the liver on active or toxic metabolites.[9,10] Thus, even the pharmacokinetics of drugs that are not excreted by the kidney may be changed in patients with kidney disease.[11] Evidence has emerged that cytochrome P450 enzymes and multiple intestinal and hepatic drug transporters have different activity or transport characteristics in uremia. Little evidence has been accumulated on the impact of kidney disease on metabolized and nonrenally cleared drugs; thus, dosing recommendations for such drugs in ESRD or otherwise reduced kidney function are mostly lacking. A nice overview of this emerging research has been compiled by Nolin and colleagues.[12]

Distribution of drugs and their metabolites may also be different in patients with CKD: edema and fluid overload, especially the cyclic changes in hydration in hemodialysis patients, may change the volume of distribution for certain drugs.[13,14] The malnutrition and subsequent hypalbuminemia often encountered in ESRD patients may further affect the distribution of highly protein-bound drugs. Further, changes of the affinity of certain drugs to plasma protein have also been described in uremia, even in the presence of normalbuminemia, additionally complicating drug therapy in these patients.[15–17] The fraction of unbound drugs may thus be increased, and toxicity may be the consequence. As noted by McIntyre and Owen, "decreased binding results in more unbound drug being available at the site of drug action or toxicity, the distribution volume is increased, resulting in lower plasma concentrations after a given dose. More unbound drug is available for metabolism and excretion, which decreases the half-life of the drug in the body."[3] Unfortunately, all these alterations in drug distribution and binding in advanced kidney disease appear rather unpredictable. Such therapeutic uncertainty is potentiated in light of the increased potential for drug-drug interaction in these patients with often highly complex medication regimens.

Although all these aspects of altered drug handling in kidney disease may not be so important in medications with a wide therapeutic window and low toxicity, patients with kidney disease may be particularly prone to experiencing toxicity from drugs with a narrow therapeutic window. It appears mandatory to require additional pharmacokinetic studies that specifically focus on nonrenal excretion and metabolization pathways for such medications with high toxicity potential. From this information, it becomes clear that prescribing medications in patients with kidney disease is not a trivial task and that special consideration will need to be given to ensure appropriate treatment in these patients. There are several references that specifically focus on recommendations for drug dosing and monitoring in patients with CKD, patients with ESRD who are on renal replacement therapy, and patients on continuous renal replacement therapy.[3]

THE CHALLENGE OF EVIDENCE-BASED PRESCRIBING IN KIDNEY DISEASE

An enormous amount of medical evidence has been accumulated that may guide our treatment decisions in the general population. It is important, however, to consider what types of patients were selected to be exposed to experimental treatment in the clinical trials that define medical practice today. It is well-known that patients enrolled into most trials, especially those of primary or secondary prevention, are usually healthier than the larger target population of the evaluated treatment. This is due to exclusion criteria in most trials based on age, perceived life expectancy at enrollment, or preexisting comorbid conditions. It has clearly been shown that kidney disease is one of the characteristics that were often used to disqualify patients from trial enrollment. Coca and colleagues reviewed all randomized controlled trials of interventions (not restricted to medications) in congestive heart failure or acute coronary syndrome that were published in 11 major general medical or subspecialty (cardiovascular or nephrology) journals from 1985 to 2005 and that enrolled at least 100 patients.[18] They found that overall 56% of trials had an explicit exclusion criteria banning patients with kidney disease from enrollment. In several trials, the exclusion criteria were vague and up to the investigator's interpretation rather than a specific cutoff in serum creatinine or glomerular filtration rate. Exclusions of patients with kidney disease were particularly common in trials of inhibitors of the renin-angiotensin-aldosterone system (94%) or in trials of anticoagulants (92%). Unfortunately, these investigators did not find a temporal trend toward greater inclusion of patients with kidney disease in more recent years. In a similar investigation, Charytan and Kuntz focused on randomized trials of specific interventions rather than clinical conditions and attempted to capture all trials of beta blockers, platelet glycoprotein GPIIb-IIIa complex, HMG-CoA reductase inhibitors ("statins"), aspirin, ticlopidine, angioplasty, and stents, independent of the size of the trial or the journal in which these appeared.[19] Similar to the impression gained from Coca's work, 75% of randomized trials explicitly excluded patients with renal insufficiency, and 80% designated patients with ESRD ineligible to enroll. This was in stark contrast with exclusion criteria for diabetes, hypertension, or smoking, which served as control "conditions" for Charytan and Kuntz study. Only three trials (4%) excluded patients

with diabetes; not a single study banned patients with high blood pressure or smoking from participation. Interestingly, of 30 trials of statins, 27 (90%) excluded patients with kidney disease and only 3 (10%) reported baseline kidney function. Thus, being faced with evidence that is derived from trials devoid of patients with kidney disease, it would require a leap of faith to trust that such evidence and the resulting guidelines for the care of the general population can be used to guide treatment of patients with CKD or ESRD. It is unclear whether such extrapolation is appropriate, and it is likely that in some instances it is appropriate whereas in others it is not.

CASE STUDY: EFFICACY OF STATINS IN PATIENTS WITH KIDNEY DISEASE

Let us examine the available evidence on the efficacy of statins specifically in patients with kidney disease. Statins have been a cornerstone of secondary and primary cardiovascular prevention in the general population for more than a decade. Several large efficacy trials in the general population and in various more restricted patient groups have been conducted and have consistently yielded beneficial results (Table 15-1).[20–24] Generally, use of statins yielded significant reductions in the risk of recurrent cardiovascular events with reported risk reductions usually exceeding 25%. Similarly, statins have also been shown to be efficacious in reducing the risk of a first cardiovascular event in patients at increased risk. In addition, it appears that more is better, aiming for greater reduction in the low-density lipoprotein (LDL) cholesterol subfraction yields greater benefits.[25,26]

As mentioned previously, however, many trials have explicit exclusion criteria for patients with CKD, and statin trials are no exception. Still, some evidence does exist on the efficacy of statins in the CKD population. Tonelli and colleagues used data from several large statin trials and took advantage of the fact that investigators do not always follow exclusion criteria strictly and some patients with higher creatinine were still enrolled. Further, creatinine-based exclusion of patients with kidney disease will not prevent some patients with CKD to be enrolled, specifically if they have certain characteristics that render their estimated glomerular filtration rate low, such as older patients. Using data from

TABLE 15-1 Placebo-Controlled Rrials of HMG-CoA Inhibitors in the General Population and in Patients with Kidney Disease

STUDY	TYPE	PERSONS	MEDICATION	BASELINE KIDNEY FUNCTION	BASELINE LDLC	LDLC CHANGE	MAJOR CORONARY EVENTS	TOTAL MORTALITY
				GENERAL POPULATION				
WOSCOPS[20]	P	6595	Pravastatin 40 mg	N.A. (maximum creatinine was 1.7 mg/dl)	192	−26%	−31%	−22%
AFCAPS/ TexCAPS[21]	P	6605	Lovastatin 20/40 mg	N.A.	150	−25%	−37%	N.S.
4S[22]	S	4444	Simvastatin 10/40 mg	N.A.	188	−35%	−35%	−30%
CARE[23]	S	4159	Pravastatin 40 mg	N.A. (maximum creatinine was 2.5 mg/dl)	139	−27%	−25%	−9% (N.S.)
LIPID[24]	S	9014	Pravastatin 40 mg	N.A. (maximum creatinine was 4.5 mg/dl)	150	−25%	−29%	−23%
Patients with Kidney Disease								
4D (HD)[33]	P/S (29% w/h/o CVD)	1255	Atorvastatin 20 mg	ESRD	126	−42%	−8% (N.S.)	−7% (N.S.)
AURORA (HD)[34]	P/S (40 w/h/o CVD)	2776	Rosuvastatin 10 mg	ESRD	100	−43%	−4% (N.S.)	−4% (N.S.)
CARE (Cl_{Cr} <75)[27]	S	1711	Pravastatin 40 mg	1.2 mg/dl	139	−27%	−28%	−19% (N.S.)
WOSCOPS/ CARE/LIPID (Cl_{Cr} 30 to 60)[28]	P/S (89% w/h/o CVD)	4491	Pravastatin 40 mg	1.4 mg/dl	165	−29%	−23%	−14%
ALERT (KTR)[29]	P/S (10% w/h/o CVD)	2102	Fluvastatin 40/80 mg	1.64 mg/dl	158	−32%	−17% (N.S.)	+2% (N.S.)

4D, Die Deutsche Diabetes Dialyse Studie; *4S,* Scandinavian Simvastatin Survival Study; *AFCAPS/TexCAPS,* Air Force/Texas Coronary Atherosclerosis Prevention Study; *ALERT,* Assessment of Lescol in Renal Transplantation; *AURORA,* A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; *CARE,* Cholesterol and Recurrent Events trial; Cl_{Cr}, creatinine clearance; *CVD,* cardiovascular disease; *ESRD,* end-stage renal disease; *HD,* hemodialysis; *KTR,* kidney transplant recipients; *LDLC,* low-density lipoprotein cholesterol; *LIPID,* Long-Term Intervention with Pravastatin in Ischemic Disease trial; *N.A.,* not reported; *N.S.,* not significant; *P,* primary prevention; *S,* secondary prevention; *w/h/o,* with history of; *WOSCOPS,* West of Scotland Coronary Prevention Study.

the Cholesterol and Recurrent Events (CARE) trial,[23] Tonelli and coworkers found that in those patients whose estimated creatinine clearance was below 75 ml/min/1.73 m^2, statins were efficacious in secondary cardiovascular prevention.[27] Forty milligrams of pravastatin reduced LDL cholesterol by 27% and yielded a 28% reduction in the risk of the primary endpoint, which was a composite cardiovascular outcome. They did not, however, demonstrate an effect on total mortality. In another project, the same investigators used data from the pravastatin pooling project, which provided person level information from three large trials that randomized patients to 40 mg of pravastatin versus placebo (CARE,[23] Long-Term Intervention with Pravastatin in Ischemic Disease [LIPID],[24] West of Scotland Coronary Prevention Study [WOSCOPS][20]). Restricting the study sample to those patients who had an estimated creatinine clearance of 30 to less than 60 ml/min/1.73 m^2, most of them from the two secondary prevention trials (CARE, LIPID), major coronary events were significantly reduced by 23% and mortality from any cause was reduced by 14%.[28] Thus, using relative risk as the metric of evaluation, it was concluded that statins were equally efficacious in patients with moderate CKD compared to the general population. The absolute risk reduction achieved with statins, however, was even greater in patients with CKD, due to the greater baseline risk in this population.

Although these analyses were subgroup analyses of trials that were conducted in the general population, trials testing the efficacy of these medications in populations with kidney disease exist as well. The Assessment of Lescol in Renal Transplantation (ALERT) trial enrolled 2102 prevalent kidney transplant recipients and exposed them to 40 mg of fluvastatin (which was increased to 80 mg after 2 years) or placebo for more than 5 years.[29] At baseline, LDL cholesterol concentrations were similar to other statin trials and active treatment was found to reduce LDL cholesterol by 32%, which is also in line with findings from the general population. The primary endpoint, however, was not affected by treatment: the 17% reduction in a composite cardiovascular endpoint in the statin arm was not significantly different from placebo ($p = 0.14$) and mortality from any cause was indistinguishable between the two groups (relative risk: +2%, $p = 0.85$). Much discussion followed the publication of these findings, especially because certain components of the composite endpoint were significantly reduced by statin treatment. The risk of cardiac death was 38% lower ($p = 0.03$) and that of definite nonfatal myocardial infarction was 32% lower ($p = 0.05$) in those randomized to fluvastatin. By contrast, the third component of the composite endpoint, cardiac intervention, appeared unaffected by treatment status. It was decided to extend follow-up in all consenting patients with 80 mg of open-label fluvastatin being offered to all patients independent of baseline treatment allocation. After another 2 years of follow-up, among the 92% of eligible patients who participated, the primary study endpoint reached significance, and those originally randomized to fluvastatin experienced a 21% lower risk of that endpoint ($p = 0.04$).[30] Needless to say that the discussions continued after these additional data became available. Critics argued that departure from the original protocol and the failure to adjust the p-value of the extension study (which would once again have been nonsignificant) rendered the results of the trial inconclusive. No data are available on how ALERT has influenced practice. Treatment guidelines had supported statin treatment in kidney transplant patients prior to ALERT, but they have yet to update their recommendations in response to the new evidence.[31,32]

Statins were also subjected to rigorous testing in randomized trials in the dialysis population. The first large trial in hemodialysis patients, the Die Deutsche Diabetes Dialyse (4D) study, enrolled 1255 prevalent hemodialysis patients who also had diabetes, which is a group of patients with very high cardiovascular risk.[33] Patients were randomized to receive either 20 mg of atorvastatin or placebo. Although the average baseline LDL cholesterol was lower than in most other statin trials until then (126 mg/dl), the 42% reduction achieved by active treatment was higher than in other studies. After the designated follow-up of 4 years, however, the primary study endpoint (composite of cardiac death, nonfatal myocardial infarction, stroke) was not significantly different between the two groups (−8%, $p = 0.37$), and death from any cause was also unaffected by statin treatment (−7%, $p = 0.33$). Again, much discussion ensued about problems with study design and whether the findings from prevalent hemodialysis patients with diabetes could be extrapolated to incident dialysis patients or to those without diabetes. As with ALERT, it remains unclear whether 4D had any impact on prevailing practice. In 2009, however, a second statin trial in dialysis patients was published. The A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) trial randomized 2776 prevalent hemodialysis patients to 10 mg of rosuvastatin or placebo and followed these patients over an average of 3.8 years.[34] This study population already had a low average LDL cholesterol level (100 mg/dl), but active treatment reduced the average level further by 43%. Such pronounced reduction in LDL cholesterol concentration, however, did not translate into clinical benefit. Neither the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke, nor mortality from any cause were affected by statin treatment (−4% for both outcomes; $p = 0.59$ and 0.51, respectively). Another large-scale statin trial is currently underway: the Study of Heart and Renal Protection (SHARP) was planned to enroll approximately 9000 patients with CKD, 6000 of whom were planned to be predialysis and 3000 to be dialysis patients.[35] These patients were randomized to receiving combination treatment with simvastatin and ezetimibe or matching placebo.

This case study clearly illustrates the difficulty with practicing evidence-based medicine in nephrology. Arguably, statins comprise the drug class with the greatest degree of trial evidence available specifically in patients with varying degree of kidney disease. The collected information, however, remains ambiguous and subject to a great deal of subjective interpretation. Whether negative findings are a consequence of suboptimal trial design, execution, or truly a reflection of absence of a meaningful benefit from statin treatment in these patients remains unclear. Unfortunately, this problem covers most of nephrology and is unlikely to be resolved anytime soon. In addition, underlying disease processes may be different in patients with CKD including ESRD compared to the general population, which may explain differences in drug efficacy across the spectrum of

kidney function.[36–39] Because nobody can know exactly which drugs have altered benefits and risks in patients with kidney disease, however, specific trial investigation of all medications in patients with CKD is desirable.

MEDICATION USE IN PATIENTS WITH KIDNEY DISEASE

Little is known about drug use in patients with kidney disease. The few reports available are usually driven by interest in kidney-disease specific drugs or drug classes, such as erythropoiesis-stimulating agents,[40] oral and intravenous iron supplements,[41] dietary phosphate binders,[42,43] oral and injectable vitamin D compounds and analogues,[44–46] oral calcimimetic agents,[47] and immunosuppressant drugs.[48–50] These studies are often driven by funding from pharmaceutical companies who are eager to compile evidence on and draw attention to their marketed drugs, preferably prior to the expiration of patent exclusivity. By contrast, extremely little data are available on the uses of other commonly used medications in patients with kidney disease. One may ask why this may be the case. The answer is not straightforward, but certain contributing factors can be identified. First, assessing medication use is generally not straightforward and may lead to different results, dependent on the method of assessment used. Often regarded the gold standard, filled drug prescriptions generate reimbursement claims that are being submitted to pharmaceutical benefits programs or other insurance carriers and can then be used to paint a rather detailed and comprehensive picture of prescription drug use for each patient over time. Such assessment is very close to the event of interest, which is the actual taking of the drug by the patient. Although it is possible that patients fill prescriptions, but then fail to take them, prescription claims constitute the type of data most closely related to this event of interest. After all, patients make their way to the pharmacy to fill their prescribed medications and often pay a copayment, which is an economic disincentive to filling a prescription with the anticipation or intention of not taking that drug. Longitudinal records of prescriptions filled can further reveal nonadherence behaviors through absence of refill events, another important aspect of maintenance drug therapy evaluation.[51] All other instruments to assess prescription drug use are comparatively error-prone and often cumbersome and expensive.[52,53] Electronic pill boxes are available, but they are impractical and relatively costly and may be manipulated by the patient. Pill counts can also be tailored by patients to reflect compliant behavior. Patient interviews or questionnaires are also limited by their cost, and the quality of the data obtained may be hampered by the information given by the patient due to desirability considerations (e.g., claiming to take the prescribed drug if in fact it is not taken) or simple forgetfulness. Similarly, abstractions of medical records are also time-consuming and expensive and may also be misleading as entered information may be inaccurate, incomplete, or not reflective of actual patient behavior. Naturally, over-the-counter medications constitute a special case. These medications do not appear in claims data and can only be ascertained using other methods.

Although representing the relative gold standard in pharmacoepidemiology, prescription claims have rarely been used for drug utilization, comparative effectiveness and safety studies in patients with kidney disease. One of the most obvious reasons is the absence of prescription claims from large databases that are often used for outcomes research in nephrology. The United States Renal Data System (USRDS) is the most widely used data source for outcomes research in patients undergoing maintenance dialysis or after receipt of a kidney transplant. Insurance claims from Medicare, the federal health insurance program for older or disabled Americans, which is mandated to pay for the healthcare of most U.S. patients with ESRD, did not cover oral prescription drugs until recently. Thus, the USRDS does not contain any claims data on prescription drug use. Only intravenous drugs administered in outpatient settings are registered in that database, because such medications are reimbursed through Medicare Part A. After the Medicare Modernization Act and the creation of Medicare Part D, oral prescription drug coverage is now available for most patients with ESRD, but the claims from this program have not yet become available for systematic pharmacoepidemiologic research in the USRDS.

In light of the absence of such important information, medication use was collected within the scope of a few special USRDS studies, most importantly the Dialysis Morbidity and Mortality Study (DMMS) Waves 2, 3, and 4.[54] Wave 2 contained prescription and over-the-counter drug information (and erythropoietin and injectable vitamin D use) in a random sample of U.S. incident hemodialysis and peritoneal dialysis patients in 1996 and 1997, as abstracted by dialysis personnel within 60 days of initiation of renal replacement therapy. Waves 3 and 4 studied prevalent hemodialysis patients at the end of 1993. The data were collected by facility personnel and entered using free text format, which made it rather cumbersome and somewhat error-prone to ascertain specific drugs for research purposes. Still, these data turned out to be useful and have been applied in several studies as discussed hereafter. More recently, the USRDS Center and its contract research affiliate have obtained and merged into the USRDS database prescription claims from large health insurance databases that contain such claims (Medstat, Ingenix i3). This combined database has been used to generate interesting reports on the use of certain drug classes, which have been made available in the Annual Data Report of the registry and published in the American Journal of Kidney Diseases. Another important source of drug use data is the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international multicenter effort on describing the practice of hemodialysis care and patient outcomes.[55] Although drug data was derived from charts rather than claims, DOPPS has generated numerous interesting pharmacoepidemiological observations that have contributed to a better understanding of medication use and associated outcomes in hemodialysis patients. More recently, dialysis providers have begun to systematically track prescription drug use and the first studies based on these databases have become available.[47,56,57] Other sources of drug information include prospectively collected data in cohorts of dialysis patients,[42] and the merger of prescription drug data from state prescription drug programs for the relatively indigent (e.g., Medicaid) with other medical claims from Medicare.[58,59]

From the available evidence, it has become clear that dialysis patients take a large number of oral medications. The

DMMS Waves provide the most comprehensive and representative picture, although these data are now slightly outdated.[54] Patients undergoing hemodialysis at the end of 1993 were found to be taking a median of nine different medications (Table 15-2). Patients initiating dialysis in 1996 and 1997 were prescribed a median of 8 medications, with 8% of patients receiving more than 15 different drugs. The median number of medications was similar in older and younger patients, in those undergoing hemodialysis and those on peritoneal dialysis; patients with diabetes appeared to be taking slightly more drugs. Table 15-2 shows the frequencies of use of several important medication classes

TABLE 15-2 Oral Medication Use in Incident U.S. Dialysis Patients (1996 to 1997)[54]

DRUG CLASS	ALL* N = 3917	HD N = 1998	PD N = 1919	COMMENT
Median number of medications	8	8	8	
Any nondiuretic antihypertensive		75%	81%	
Calcium-channel blockers		52%	56%	
ACE-inhibitors		24%	29%	
Beta blockers		17%	21%	
Central α_2-receptor agonists		14%	16%	
Peripheral α_1-receptor blockers		10%	12%	
Other (nondiuretics)		7%	7%	
Nitrates		22%	17%	
Digoxin		13%	11.4%	May include data from DMMS Waves 3 and 4
Lipid-lowering agents		8%	15%	
Statins	9.7%			[98]
Fibrates	2.1%			[98]
Any phosphate-binder		78%		
Calcium-containing phosphate binder		75%	81%	Calcium acetate and carbonate were used by similar proportions of HD, but calcium carbonate was used in much higher proportion among PD patients
Aluminium-containing phosphate binder		6.1%		4% of HD patients used both an aluminium- and a calcium-based binder
Vitamin D analogues		42.2% (35.1% IV, 7.9% oral)	32.9% (1.1% IV, 30.6% oral)	
Iron		51% (8% IV, 45% oral)	61% (1.9% IV, >59% oral)	Few patients received both intravenous and oral iron
H2-receptor antagonist or proton pump inhibitor		30%	26%	
Motility agent	13%			Unclear whether this includes patients from DMMS Waves 3 and 4
Analgesics		12%	9%	<1% received more than one analgesic
Narcotics		5.6%	3.8%	
NSAIDs (excludes ASA)		1.7%	1.9%	
Other nonnarcotics		5.1%	3.7%	
Aspirin		18.5%	17%	
Warfarin		6.5%	5.7%	
Oral hypoglycemic		11.7%/13.8%		Among patients in whom diabetes was listed as the cause of ESRD (<65/65 years of age or older)
Insulin		56.5%/46.3%		Among patients in whom diabetes was listed as the cause of ESRD (<65/65 years of age or older)
Thyroid replacement		10%	11%	
Antidepressants		12%		Not substantially different between HD and PD
Benzodiazepines	7.9% (13.5%)	8.2%	7.6%	In a cleaner sample of 3630 patients, 13.5% were reported to take a benzodiazepine or zolpidem[115]
Multivitamins		64%	67%	

*Where not specifically reported, overall use was calculated from reported HD- and PD-specific proportions using weighted means for the underlying sampling scheme that selected all PD patients and a random 20% sample of all HD patients in the participating facilities. Facilities were randomly selected from all U.S. facilities on the Master List of Medicare Approved Dialysis Facilities as of December 2003 plus all newly opened facilities after January 2004. Small rounding errors are possible.

in incident U.S. dialysis patients (on or around day 60 of dialysis), which were compiled from the USRDS report and other studies that used the DMMS Wave 2 database.

Even fewer systematic studies of medication use and associated outcomes have been conducted in CKD patients who have not yet reached ESRD. Claims databases are suboptimal, because they usually do not contain data on creatinine or urine protein, which are mandatory to define presence and stage of CKD. Thus, CKD needs to be ascertained from diagnosis codes that are listed on inpatient or outpatient claims. Validation studies have shown that approaches to use such diagnosis codes from medical claims have rather good sensitivities of correctly identifying patients with an estimated GFR of less than 60 ml/min/1.73 m^2, but the specificities were rather poor.[60–62] It is unclear whether studies in those identified as having CKD can generate results that are generalizable to those that were not captured by the claims-based algorithm (i.e., the false negatives). It is further unclear whether the results from this validation exercise, which was conducted in older, indigent patients who were admitted for a suspected heart attack, can be generalized. It is possible, if not likely, that the sensitivities and specificities of claims-based approaches to identify patients with CKD are quite different in other populations. In addition, no stratification by CKD stage is possible, although an October 1, 2005 revision to the International Classification of Diseases contained the addition of a qualifier, a fourth digit that would indicate CKD class. From preliminary work, it appears that these stage-specific codes are highly underused and that most CKD codes remain in three-digit format.[63] These revised stage-specific codes have not yet been validated regarding their ability to accurately reflect estimated GFR.

Other databases that can support drug use and pharmacoepidemiological studies are integrated medical record systems of certain closed-panel health-maintenance organizations (e.g., Kaiser Permanente) or the Veterans' Affairs system. Kidney function can be ascertained from laboratory measurements. Both databases have been used for interesting pharmacoepidemiological studies, although much more evidence from such databases can be expected in the future.[64,65]

Among all oral prescription medications, the ones whose use has received the most attention are inhibitors of the renin-angiotensin-aldosterone system (RAAS). Both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended for use in patients with proteinuric kidney disease from diabetes and their appropriate use constitutes a quality indicator.[66] Underuse of these medications in patients with diabetes have been reported from several populations and seem to be especially prevalent among the elderly.[64,67–69] Such underuse has also been described also in patients with concomitant heart failure and renal dysfunction, both in a general population and in older patients.[70,71] Most of these studies found that roughly only half of eligible patients received these recommended therapies, and more reduced kidney function was often predictive of lower use.

Another frequently-studied topic is the use of recommended medications for secondary prevention after myocardial infarction. It had been observed by Chertow and others that patients with CKD or ESRD who were hospitalized with an acute coronary syndrome experienced lower use of acute diagnostic and therapeutic interventions, such as angiography and percutaneous transluminal angioplasty, compared with patients without ESRD.[72,73] Inpatient use of thrombolysis and medications such as aspirin and beta blockers was also lower in patients with kidney disease compared to those without it.[65,73–77] In studies that used several strata of kidney function, receipt of these interventions was monotonically lower in those with worse CKD. Similarly, patients surviving and being discharged from hospitalization for myocardial infarction tended to experience lower outpatient use of beta blockers, statins, and inhibitors of the RAAS if they had worse CKD compared to patients with more normal kidney function.[58,59]

Although the majority of pharmacoepidemiological research in nephrology has focused on cardiovascular oral medications and inhibitors of the RAAS in patients with diabetes, few studies are available on other commonly used drugs. These include studies of gastrointestinal medications,[78,79] analgesics and aspirin,[80–82] diuretics,[83] and vitamins,[84] to name a few. A handful of investigations has provided a more comprehensive picture of medication use in general in patients with kidney disease.[54,85–88]

Practically no systematic information is available on medication use in kidney transplant recipients, which is remarkable given the expected high burden of transplant-related medications alone, immunosuppressants, preventive or therapeutic antivirals and antibiotics, and other medications for the numerous comorbidities that these patients experience. Studies on immunosuppression use in kidney transplant recipients are certainly abundant, thanks to the availability of such information in large registries, but little attention has been given to other prescription drug classes. A single center study from Georgia found that, on average, 11.3 medications were prescribed to a random sample of their patient population, with older patients taking more drugs than younger transplant recipients (12.4 versus 10.3).[89] An important pharmacoepidemiological program is also underway at the Medical University of Vienna, Austria, where patients' clinical records have been merged with prescription drug claims from the sickness-funds in which they were enrolled.[90–92] Because Austria provides universal healthcare to its residents, a comprehensive picture of prescription drug use could be painted.

EFFICACY, EFFECTIVENESS, AND SAFETY OF MEDICATIONS IN KIDNEY DISEASE

Why has it been it so difficult to build evidence guiding optimal care of patients with kidney disease? One aspect is the exclusion of these patients from large efficacy trials as described previously. There is another aspect to this, however, that has nicely been studied by Strippoli and colleagues at the Cochrane Renal Group.[93] These researchers compared the trial evidence that had been accumulated from 1966 to 2002 in the field of nephrology versus 12 other major subdisciplines of internal medicine. During that time period, nephrology had the fewest randomized trials of all internal medicine subspecialties: 2779 compared to the second lowest count, 5335 in hematology; cardiology had the most trials, 27,109. They identified certain areas with a particularly few trials such as glomerulonephritis, whereas relatively more trials were conducted in kidney transplant recipients

and dialysis patients. In relation to all scientific reports within nephrology, the proportion of trials was lowest in acid-base disorders and glomerulonephritis, whereas it was above average in urinary tract infection, diabetic nephropathy, and transplantation. Even more concerning was the quality of the published trials. Reports of allocation concealment were uncommon (7.4%), as was blinding of participants and investigators. Half of the trials did not report whether they performed an intention to treat analysis, whereas 30% did and 20% did not use such a standard approach to analysis.[93] In addition, it appears that several large and important trials in nephrology failed to reject the null hypothesis of no effect. Although a null finding is certainly always a possibility, it seems that many of these studies suffered from reduced statistical power. Often, power calculations were later proven to be off the mark due to assumptions of key parameters that were not reflected in the actual trial: lower observed event rates than anticipated, competing risks that were not fully considered, greater cross-over among treatments than anticipated, especially drop in from already marketed products, greater than expected nonadherence with assigned therapies or dropouts. In several cases, it was attempted to rescue some of the investment by focusing on post hoc analyses, trial extensions, and subgroup analyses, often leading to even greater controversy than before. It is regretful that the large investments that were made in these few large-scale trials in patients with kidney disease were unable to provide conclusive evidence.

Quite a few pharmacoepidemiological studies have been conducted in patients with CKD or ESRD and related certain medications with patient outcomes. Most of these studies have used the information available in the DMMS Waves and in DOPPS. Because cardiovascular mortality is so important in patients with ESRD, several studies have evaluated the associations of the uses of various cardiovascular medication classes with outcomes in these patients.[59,70,94–106] Most of these analyses focused on the associations between uses of recommended medications after myocardial infarction and mortality. Wetmore and Shireman have recently reviewed this body of evidence, focusing on beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers.[107] Including randomized trials, they identified only 17 unique reports, but 14 of these were observational studies. Table 15-3 presents this evidence and also contains information on the associations with clinical outcomes of aspirin and statin use.

A single randomized, placebo-controlled trial had tested angiotensin-converting enzyme inhibitors in prevalent hemodialysis patients with left-ventricular hypertrophy, the Fosinopril in Dialysis Study. Over 2 years of follow-up, the incidence of the combined cardiovascular study endpoint did not differ between the treatment groups (RR = 0.93; 95% CI: 0.68 to 1.27). Among the observational studies, those based on DMMS Wave 2 data were also unable to find an association between angiotensin-converting enzyme inhibitors and overall mortality, cardiovascular mortality, hospitalization for heart failure, or hospitalization for acute coronary syndrome in incident dialysis patients.[56,94,96,97,99,100] The DMMS Wave 2 cohort did not specifically select patients with previous cardiovascular disease, but rather reflected a representative sample of new U.S. dialysis patients. Several of the studies based on other data, such as the Collaborative Cardiovascular Project or Medicare claims, however, did find protective associations between use of inhibitors of the RAAS system and mortality after acute myocardial infarction.[59,70,104,105] No randomized trials have tested the efficacy of aspirin in dialysis patients, but several observational studies have evaluated the association between aspirin use and cardiovascular outcomes or mortality. Most studies did not find an association, but Ishani and Chan found increased mortality rates among incident dialysis patients who used aspirin.[56,96] Berger, by contrast, found a lower 30-day mortality among dialysis patients who received aspirin during their hospitalization for myocardial infarction.[70] Treatment with beta blockers was tested in one small randomized trial of carvedilol in hemodialysis patients with congestive heart failure. In 114 patients, carvedilol treatment led to a 51% reduction in all-cause mortality and a 68% reduction in cardiovascular mortality.[108] Unfortunately, there are several methodological issues with this study as discussed by Wetmore and Shireman.[107] Observational studies were mostly negative,[59,94–97,99,100,103–106] but a study of prevalent dialysis patients revealed a 22% reduction in all-cause mortality among existing beta blocker users, which was of borderline significance.[101] Berger found lower 30-day mortality among patients who received beta blockers during their hospitalization for myocardial infarction.[70] There was some evidence on the potential benefit of calcium channel blockers from a trial that included protocol assignment to nitrendipine in dialysis patients, but again, several methodological issues limit the applicability of these results.[109] Of all observation studies of calcium channel blockers in dialysis patients,[70,94,95,97,99–101,104,106] a single one revealed a significant association. Ishani found a 10% reduction in a combined cardiovascular outcome among incident dialysis patients using calcium channel blockers.[96] There is some evidence that this association may have been driven by nondihydropyridine calcium channel blockers.[95] As mentioned previously, two large randomized, placebo-controlled trials failed to find a protective effect of statins on cardiovascular outcomes in dialysis patients.[33–34] Although most observational studies did not find an association between statin use and outcomes, either,[59,96,99,100,103] the study by Seliger and colleagues revealed a strong protective association between statin use in incident dialysis patients and mortality from any cause (32% reduced risk) or from cardiovascular cause (37% reduced risk).[98] Although this pharmacoepidemiological analysis was able to control for a large number of important potential confounders, including indicators of frailty, these findings are discrepant to the evidence from randomized experiments. One key difference between Seliger's study population and the ones included in 4D and AURORA is that the trials enrolled patients who had been undergoing dialysis for years, on average, whereas patients in the DMMS Wave 2 were incident on renal replacement therapy. It is possible that the efficacy or effectiveness of statins changes by duration of dialysis treatment, but formal analyses on this matter have not yet been published.

As one can gather from this evidence, which is not necessarily sparse, the findings of the various studies are not giving any compelling direction for any of these cardiovascular drug classes. This may be attributable to small sample sizes, suboptimal medication assessment mostly from chart abstraction, unavailability of longitudinal records of medication use to distinguish exposed and unexposed time periods, and methodological shortcomings. Clearly, subsequent studies will need to address these issues. Furthermore, similar

TABLE 15-3 Outcomes Associated with Uses of Cardiovascular Medications in ESRD Patients from Observational Studies

AUTHOR/YEAR	RAAS INHIBITORS	ASPIRIN	BETA BLOCKERS	CALCIUM-CHANNEL BLOCKERS	STATINS
DMMS Wave 2					
Abbott et al., 2004[94]	De novo hospitalization for heart failure: 0.97 (0.76-1.23); the above or cardiac death: 0.91 (0.74-1.13)	De novo hospitalization for heart failure: 1.02 (0.70-1.49); the above or cardiac death: 1.01 (0.73-1.39)	De novo hospitalization for heart failure: 0.69 (0.52-0.91); the above or cardiac death: 0.77 (0.61-0.97)	De novo hospitalization for heart failure: 0.94 (0.77-1.15); the above or cardiac death: 0.95 (0.8-1.12)	
Griffith et al., 2003[95]			Mortality: 0.94 (0.83-1.07); CV mortality: 1.05 (0.89-1.25)	Mortality: DHPs: 0.94 (0.84-1.06); Non-DHPs: 0.87 (0.75-1.01); CV mortality: DHPs: 0.93 (0.78-1.1); Non-DHPs: 0.78 (0.62-0.97)	
Ishani et al., 2004[96]	Combined CV outcome: 0.99 (0.9-1.09)	Combined CV outcome: 1.13 (1.02-1.25)	Composite CV outcome: 0.95 (0.85-1.06)	Combined CV outcome: 0.9 (0.82-0.98)	Combined CV outcome: 0.87 (0.76-1.01)
Kestenbaum et al., 2002[97]	Mortality: 0.96 (0.82-1.13); CV mortality: 0.9 (0.71-1.14)	Mortality: 0.95 (0.79-1.13); CV mortality: 1.13 (0.88-1.44)	Mortality: 1.03 (0.87-1.22); CV mortality: 1.02 (0.79-1.31)	Mortality: 0.79 (0.69-0.9); CV mortality: 0.74 (0.6-0.91)	
Seliger et al., 2002[98]					Mortality: 0.68 (0.53-0.86); CV mortality: 0.63 (0.44-0.91)
Trespalacios et al., 2002[99]	ACS hospitalization: N.S.; Mortality after ACS: N.S.	ACS hospitalization: N.S.; Mortality after ACS: N.S.	ACS hospitalization: N.S.; Mortality after ACS: N.S.	ACS hospitalization: N.S.; Mortality after ACS: N.S.	ACS hospitalization: N.S.; Mortality after ACS: N.S.
Trespalacios et al., 2003[100]	Heart failure (de novo or recurrent) hospitalization: N.S.	Heart failure (de novo or recurrent) hospitalization: 1.56 (1.13-2.15)	Heart failure (de novo or recurrent) hospitalization: N.S.	Heart failure (de novo or recurrent) hospitalization: N.S.	
DMMS Waves 3 & 4 Study					
Foley et al., 2002[101]	Mortality: 1.05 (0.96-1.17)		Mortality: 0.84 (0.75-0.93)	Mortality: 1 (0.94-1.07)	
Other databases					
Berger et al., 2003[70]	Mortality: 0.58 (0.42-0.77)	Mortality: 0.64 (0.5-0.8)	Mortality: 0.78 (0.6-0.99)	Mortality: N.S.; CV mortality: N.S.	
Boger et al., 2005[102]	Mortality: 1.07 (0.84-1.37)				
Chan et al., 2009[56]		Mortality: 1.06 (1.01-1.11)			
Chow et al., 2003[103]	Mortality: N.S.	Mortality: 0.81 (0.48-1.38)	Mortality: N.S.		Mortality: N.S.
Efrati et al., 2002[104]	Mortality: 0.48 (0.25-0.91)		Mortality: N.S.	Mortality: N.S.	
McCullough et al., 2002[105]	Mortality: 0.63 (0.47-0.83)		Mortality: N.S.		
Tepel et al., 2002[106]	Mortality: N.S.		Mortality: N.S.	Mortality: 0.33 (0.17-0.67)	
Winkelmayer et al., 2006[59]	Mortality: 0.7 (0.5-0.98)		Mortality: 1.05 (0.78-1.43)		Mortality: 0.97 (0.65-1.45)

(Modified and expanded from J.B. Wetmore, T.I. Shireman, The ABCs of cardioprotection in dialysis patients: a systematic review, Am. J. Kidney Dis. 53 (2009) 457–466.)
The reported numbers represent multivariate-adjusted relative risks and their corresponding 95% confidence limits.
ACS, acute coronary syndrome; *CV,* cardiovascular; *DHP,* dihydropyridines; *N.S.,* not significant; *RAAS,* renin-angiotensin-aldosterone system.

issues pertain to medication related outcomes research in CKD and kidney transplantation, where studies have also been sparse. In addition, studies of medication adherence in patients with kidney disease are also very scarce. A focus on adherence is warranted especially in kidney disease and the associated polypharmacy that these patients experience. It is likely that patients with kidney disease are less adherent with prescribed medication regimens, but much more needs to be learned about this important aspect of pharmaceutical therapy.

NEW APPROACH TO STUDYING MEDICATIONS IN POPULATIONS WITH KIDNEY DISEASE

From all these aspects pertaining to medications in individuals with CKD including those requiring renal replacement therapy and individuals living with a functioning kidney transplant, it becomes quite evident that novel approaches, new initiatives are needed to develop an evidence base that would allow us to practice on proven grounds in these patients. Most desirably, such information would come from randomized, controlled trials, which could provide the highest possible level of evidence. It is unrealistic to expect, however, that such trials would be funded or conducted even for the most burning aspects of clinical care in these populations, at least not within a reasonably short time frame. As a start, regulatory bodies could require that sponsors of large randomized trials include sufficient numbers of patients with advanced kidney disease, so that formal statistical tests of interaction can be conducted of *a priori* hypotheses that efficacy of the compared therapeutics do not differ by kidney function. Then again, such mandates would require much larger sample sizes to provide interaction tests with adequate power.

One possible alternative is a greater investment into observational research that would compare the effectiveness of various treatments that can be used for a specific clinical scenario. Unfortunately, this seems to be a tradeoff that is also problematic. As shown earlier, such research generates associations that may or may not be causal. If conducted on large databases containing high-quality and granular demographic, socioeconomic, clinical, and health-system information, modern epidemiological methods can be applied and comparative effectiveness questions can be asked. Large and highly detailed databases are capable of supporting novel and sophisticated research methodology, including marginal structural models and instrumental variable approaches. It will be necessary to approach each question with different methods and using different databases and if the findings are consistent, the confidence in their accuracy will be increased. Only few comparative effectiveness studies were replicated in experimental trial settings, often concurrently, and sometimes have confirmed the observational finding. For example, the increased cardiovascular risk from the use of rofecoxib or the adverse outcomes of protamine use during coronary artery bypass grafting were first shown in observational research, then confirmed in randomized trials.[110–114] Thus, an opportunity exists to fill some of the critical evidence gaps in nephrology in a cost-effective manner and to then subject important signals from such studies to the rigor of randomized trials. In order to produce such evidence that can then be translated into health policy, funding prioritization, or clinical recommendations, only the very highest research standards can be acceptable. Only this way, we will be able to improve evidence-based patient care of the vulnerable patients served by our discipline.

A full list of references are available at www.expertconsult.com.

Chapter 16

DEPRESSION AND NEUROCOGNITIVE FUNCTION IN CHRONIC KIDNEY DISEASE

Daniel Cukor, Ph.D., Deborah S. Rosenthal, M.A., and Paul L. Kimmel, M.D.

Part I
Depression in Chronic Kidney Disease Etiology of Depression

Depression has long been identified as the primary mental health issue for patients with chronic kidney disease (CKD).[1–6] To develop a full understanding of why this group has a particular vulnerability to depression and the interaction that depression has with CKD, one must explore the biological, psychological, and social context in which the depression develops. The biopsychosocial model[7] proposes that various etiological factors all play a role in establishing vulnerability to depression. The diathesis-stress model[8] posits that depression results when preexisting vulnerability is activated by stressful life events. This predisposition can be either genetic,[9] implying an interaction of nature and nurture, or cognitive,[10] involving a lasting influence of attitudes and beliefs formed in childhood.

Several biological theories for vulnerability to depression have been proposed. In its current form, the monoamine hypothesis postulates that a deficiency of certain neurotransmitters is responsible for the features of depression. According to this hypothesis, depression can arise when low serotonin levels promote low levels of norepinephrine, another monoamine neurotransmitter.[11] This hypothesis, despite explaining the mechanism of action of serotonin reuptake inhibitors, has not held up to further inquiry.[12] There appears to be little evidence of primary dysfunction of a specific monoamine system in patients with major depressive disorders, and experiments that cause the reduction of monoamines have shown that this depletion neither causes depression in healthy people nor worsens symptoms in depressed patients.[13]

Another possible biological explanation is the link between depression and neurogenesis of the hippocampus, a center for mood and memory.[14,15] The loss of hippocampal neurons is found in some depressed individuals and correlates with impaired memory and dysthymic mood. Antidepressants increase serotonin levels in the brain, which may stimulate neurogenesis and increase the total mass of the hippocampus, restoring mood and memory.[16] Similarly, magnetic resonance imaging (MRI) scans of patients with depression have detected a strong evidence of smaller hippocampal volumes and increased numbers of hyperintensive lesions compared to healthy controls.[17] These types of lesions have been associated with increased age and a higher probability of depression. Such lesions may also explain some

of the neurocognitive impairment associated with depression and old age.[18]

Other proposed biological explanations for depression include known side effects of commonly prescribed medications for end-stage renal disease (ESRD) or common comorbid illnesses,[19] an overactive hypothalamic-pituitary-adrenal (HPA) axis,[20] hormonal dysregulation,[21] and certain vitamin deficiencies.[22]

It is difficult to estimate the increased biological risk of CKD patients for the development of depression; however, the increased prevalence of vascular disease[23] could act as a predisposing biological factor.

People may also develop a psychological vulnerability to depression through noxious learning experiences. Beck developed the cognitive model of depression in which he proposed three concepts as the hallmarks of depression: a triad of negative thoughts that comprise a negative bias about oneself, one's world, and one's future; distorted information processing and recurrent patterns of depressive thinking; and distorted cognitive schema.[24] These patterns of maladaptive thinking often begin in childhood or adolescence and serve as a risk factor for the future development of the full depressive syndrome.[25]

Life on dialysis for patients with ESRD is quite demanding. It shares similarities with other chronic disorders, but beyond the loss of kidney function, there may be other substantial losses associated with ESRD. Patients can undergo profound changes in their role functioning, work status, autonomy, intimate relationships, and body image.[1] The treatment burden of hemodialysis (HD) is also demanding. The weekly time demand is substantial and lifelong, barring a successful transplantation. Patients with ESRD are highly symptomatic and report high levels of fatigue, pain, sexual dysfunction, gastrointestinal symptoms (nausea, vomiting, and anorexia), dermatological issues, and appetite changes.[26] These ongoing challenges of living with CKD can serve as the "trigger" that interacts with the person's previous vulnerabilities and induce depression. There are a variety of psychological pathways in which the challenges of ESRD can affect a person. It is possible that patients with ESRD are put into a state of "learned helplessness" because treatment options are limited, and they are forced indefinitely to remain in their difficult situations with little hope for improvement or control over their outcomes.[27] The threats to the patient's autonomy and control,[28] as a result of the demanding course of treatment, can serve as the precipitating stressor for a depressive episode.

The onset of depressive symptoms and depression can also be associated with changes in interpersonal factors, including strained or critical personal relationships. Patients with CKD may experience changes in social role functioning, relationships with a spouse or adult children as a result of the transition to a caregiving or careneeding role, the death of a significant other, or the availability or quality of social relationships with friends because of their own health-related life events.[29] These types of change have been associated with late life depression.[30]

EPIDEMIOLOGY OF DEPRESSION

The precise definition of *"depression"* as a construct, mood state, or a clinical syndrome is difficult because the feelings of sadness and hopelessness are ubiquitous and are not unique to depression or even any specific mental health problem.[31] The Diagnostic and Statistical Manual of Mental Disorders (DSM)[32] defines depression by the presence of specific symptoms in the absence of a range of other symptoms presenting for a specified duration. The hallmark symptoms of depression are low mood and loss of interest or pleasure in formerly enjoyable activities. In the current edition of the DSM (DSM-IV-TR), mood disorders with depression are divided into unipolar and bipolar depressions. The latter includes a manic component. The most common form of depression is major depressive disorder, which is characterized by the presence of a major depressive episode in the absence of mania. The hallmark features of a depressive episode must occur during the same 2-week period but are often difficult to distinguish from the common symptoms of uremia (see Table 16-1).

TABLE 16-1 Symptom Overlap Between Major Depressive Episode and Uremia

DSM-IV major depressive episode	Uremia
Depressed mood	Irritability, cognitive changes, encephalopathy, drug effects
Decreased interest in activities	Decreased libido, cognitive dysfunction
Weight change	Anorexia, edema, cachexia, volume overload
Sleep changes	Insomnia, sleep apnea
Psychomotor agitation	Encephalopathy
Fatigue	Fatigue, anemia
Diminished ability to concentrate	Cognitive dysfunction, malaise
Feelings of worthlessness	-
Thoughts of death/suicide	-

DSM, Diagnostic and Statistical Manual of Mental Disorders.

To diagnose a major depressive episode, the clinician must determine whether the depressed mood has been of a significant intensity for a 2-week duration. The clinician should explicitly inquire about each of the symptoms in Table 16-1 and then must use his or her discretion to determine whether the symptoms meet the criteria. A major depressive episode represents a significant change in the patient's functioning. Other diagnoses, such as dysthymia or an adjustment disorder, may be more appropriate for more chronic or less severe presentations.[32]

DIFFERENTIATING DEPRESSION FROM MEDICAL ILLNESS

The task of distinguishing depression from subclinical mood dysregulation is made more complex by the overlap of the symptoms of depression and ESRD.[33–35] The clinician must pay careful attention to the etiology, nature, and timing of the presentation, because there is a considerable overlap between the somatic symptoms of depression and those of uremia. The depressive symptoms of psychomotor agitation or retardation, decreased appetite or weight change, sleep disturbance, and aches and pains are often difficult to

TABLE 16-2 Beck Depression Inventory Items, with Somatic Items Italicized

1. Sadness	12. Loss of interest
2. Pessimism	13. Indecisiveness
3. Past failure	14. Worthlessness
4. Loss of pleasure	15. *Loss of energy*
5. Guilty feelings	16. *Changes in sleep*
6. Punishment feelings	17. *Irritability*
7. Self-dislike	18. *Changes in appetite*
8. Self-criticalness	19. *Concentration difficulty*
9. Suicidal thoughts or wishes	20. *Tiredness or fatigue*
10. Crying	21. *Loss of interest in sex*
11. Agitation	

distinguish from the uremic symptoms of encephalopathy, anorexia, sleep apnea, and neuropathy, respectively, adding to the difficulty of an accurate diagnosis (see Tables 16-1 and 16-2).[1,34,35]

PREVALENCE

The difficulty in defining and identifying depression has led to challenges in its standard measurement. There is still no universal standard for the most appropriate screening technique. Different studies alternatively use the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HAM-D), the Zung Self-Rating Depression Scale, subscales from the SF-36, and questions from the Kidney Disease Quality of Life (KDQOL) Instrument.[1] To provide a validating clinical diagnosis, researchers have used the Structured Clinical Interview for the DSM-IV (SCID), the Diagnostic Interview Schedule (DIS), or the Primary Care Evaluation of Mental Disorders (PRIME-MD). The field still needs to arrive at a universal consensus as to the appropriate screening and diagnostic tools for the broad population of patients with ESRD. Furthermore, there is an urgent need to precisely identify appropriate screening measures' cutoff scores that have meaningful prognostic value in varying ESRD samples.

A few studies have begun this task by validating the BDI against structured psychiatric interviews in an effort to determine a meaningful cutoff score for ESRD populations. In a sample of 99 white HD patients, Craven and colleagues[36] found a high prevalence of depression (45.4%) when using the BDI cutoff score of 10 but found that a BDI score of 15 or greater had better sensitivity and specificity for the diagnosis of depressive disorders in dialysis patients when the DIS was used as the criterion. Watnick and colleagues[37] validated the BDI and the Patient Health Questionnaire-9 against the SCID as depression assessment tools in an ethnically diverse dialysis population in several dialysis centers. Twenty-six percent of the sample was diagnosed with a depressive disorder. The optimal BDI cutoff value that maximized sensitivity and specificity was 16, whereas the optimal cutoff for the Patient Health Questionnaire was 10. Hedayati and colleagues[38] compared the BDI and the Center for Epidemiologic Studies Depression Scale (CES-D) to the SCID.[39] The prevalence of depression was 27% in their sample of 98 ethnically diverse patients. About one quarter of the subjects were veterans. A BDI cutoff score of 14, and a CES-D score of 18 had the most predictive value. These studies indicate an emerging consensus that there is an agreement between the BDI and clinician administered diagnostic tools, and a BDI score of 14–16 is predictive of depression.

Other studies report varying rates of depression, depending on the sample population and the measurement tool. A study of mostly white patients starting home dialysis in the U.S. Midwest found the prevalence of depression to be 18% using diagnostic criteria.[40] Kimmel and colleagues studied primarily African American patients with ESRD in HD centers in Washington, DC. About half of the patients scored greater than 10 on the BDI.[41–44] When the more conservative cutoff of 15 was used, about 25% of the patients were screened as positive.[43] In their sample of primarily African Americans in Brooklyn, New York, Cukor and colleagues[45] found that more than 70% of HD patients had some psychiatric diagnosis by the SCID, and 29% of the sample had a current depressive disorder.

To develop an accurate picture of depression, it is possible that longitudinal assessments provide valuable information. As a follow-up study, Cukor and colleagues reassessed subjects 16 months later, and three different clinical pathways emerged.[46] About half of the patients did not have a psychiatric diagnosis at either baseline or follow-up, one subset (21%) had a variable or intermittent course, and one subset (11%) had a persistent course, with depression diagnoses at both evaluations. The persistent course of depression was associated with a significantly lower quality of life and more reported health problems. Kimmel and colleagues[42] and Bouleware and colleagues[47] demonstrated that associations with outcomes existed with multiple measurements of depression that did not exist with baseline data. These data suggest that a single measure of depression at a specific time might not be as meaningful as measuring depression over the course of a time span.

Beyond the timing of the assessment, the demographics of the patient need to be taken into account. Specifically, the patient's gender and race need to be evaluated. In broad samples, women are believed to have higher rates of depression and go to the hospital for treatment more frequently.[48,49] It is unknown whether this pattern holds true in the U.S. ESRD population. This can be confirmed through large epidemiological studies only. Race and age have also been identified as factors in the likelihood of depression developing in patients with diabetes,[50] a primary cause of ESRD. Ethnicity has also been associated with a variety of barriers to care, leading to mental health disparities.[51,52] There is some evidence within the ESRD literature that quality of life,[53–55] perceptions of religious support,[56,57] and quality of social support vary according to race and might contribute to depression. One recent study[58] compared 78 black and 82 white HD patients and found no differences in their levels of depressive affect. They did, however, find a stronger emphasis on religion/spirituality as a coping tool within a group of black patients.

SEQUELAE OF DEPRESSION

Patients with ESRD who are also depressed are at risk for consequences that extend far beyond disordered mood. Depression can impact the course of disease progression through direct and indirect pathways.

Suicide

The most acute danger that depression presents is the increased risk of suicide. Patients with ESRD may be particularly at risk because they can commit suicide through passive means, by no longer receiving dialysis or by manipulating a functional vascular access site. This makes suicide in this population readily available and complicates assessment and intervention strategies. A recent study estimated that patients with ESRD had an 84% increased rate of suicide compared to the general U.S. population.[59] Important risk factors for suicide in the ESRD population include a previous history of mental illness, recent hospitalization, age greater than 75 years, male gender, white or Asian race, and alcohol or drug dependence. Because of the increased prevalence and the relative ease with which patients with ESRD can commit suicide, screening for depression and suicidal ideation must be an essential part of the treatment plan in patients with ESRD.[60]

Malnutrition

A possible route through which depression could impact the course of ESRD is through malnutrition. Some exploratory studies have found negative correlations between BDI scores and serum albumin levels, protein catabolic rate, and nutritional status scores in small samples,[61,62] whereas others have not.[63] The reasons for these disparate findings remain unclear but may be related to differences in composition of the study samples, cultural and socioeconomic factors, or treatment conditions.[64] The causal associations between increased depressive affect and decreased appetite or nutrition have not yet been determined but may be bidirectional. Careful longitudinal or intervention studies will be needed to establish causal relationships.

Treatment Compliance

Another route through which depression can exert an influence on ESRD outcomes is through impairing treatment compliance. Better adherence to the HD prescription has been associated with improved survival.[43,65,66] Studies[67,68] have indicated a relationship between depressive affect and laboratory and behavioral markers of poor compliance in dialysis patients. Decreased behavioral compliance with the dialysis prescription correlated with increased depressive affect in prevalent HD patients.[66,67]

Social Support

Patients with depression are more likely to feel less connected to their existent relationships and isolated from social connections. In chronic illness, this can lead to deleterious consequences. Several studies have shown an association between survival and perception of social support in patients with ESRD of different ethnic backgrounds.[43,65,69–73] McClellan and colleagues used a prospective design and demonstrated that social support predicts survival of HD patients.[73] Christensen and colleagues showed that a social support indicator as measured by family cohesion predicts survival in HD patients.[70] The result of these studies remain tentative because the effects of medical and treatment parameters were not controlled. Kimmel showed increased perception of social support, measured by the Multidimensional Scale of Perceived Social Support, predicted survival even when variation in age, severity of comorbid illness, level of serum albumin, dialysis membrane type, and study site were controlled.[43]

Immunological Response

Depression may affect the course of ESRD through its impact on immunological factors and inflammation. Stress has long been linked to the dysregulation of the HPA axis,[1,74] and depression has also been associated with abnormal glucocorticoid metabolism in healthy people.[75] The precise mechanisms through which depression may modulate the immune system are still unclear, but one proposed theory is that depression increases cytokine activity, which may disrupt the HPA axis by impairing negative feedback of circulating corticosteroids.[20,76]

There is also some evidence that inflammatory biomarkers, such as proinflammatory cytokines and C-reactive protein, are dysregulated and predict outcome in patients with ESRD.[77,78] The reasons for the increased risk of chronic inflammation in ESRD are complex; however, it has been suggested that a proinflammatory state is intrinsic to ESRD and is related to the higher-than-expected rates of cardiovascular disease and other causes of increased mortality in this population.[23]

Mortality

There has been significant scientific discussion about the association between depression and mortality in patients with ESRD. Some initial studies in these patients[79–82] found an association between depressive affect and mortality. However, these studies were preliminary and used comparisons of means between groups of deceased and surviving patients without accounting for confounding medical and demographic factors. More recent studies had generally been unable to detect simple associations between depression or depressive affect and survival in patients with ESRD.[43,65,83–86] The Dialysis Outcomes and Practice Patterns Study,[87] which followed a large multinational sample, has provided important information regarding screening questions related to depressive affect and survival in patients with ESRD and treated with HD. They used statements from the KDQOL regarding depressive affect and found that those who answered affirmatively to having more frequently experienced depressive affect had a higher risk of mortality, withdrawal from dialysis therapy, and hospitalization. Despite the nature of their nonstandard assessment, the study findings seem to indicate a robust relationship between depressive affect and medical sequelae.

Kimmel and colleagues were initially unable to demonstrate a relationship between increased level of baseline depressive affect and mortality in a sample of almost 300 HD patients. They did report associations between the

perception of increased burden of illness and mortality and between the perception of a high level of social support and improved survival.[43] More recently, the group performed longitudinal assessments of the study population, evaluating BDI scores up to six times over a period of 20 months to 5 years (mean 38.6 months). The data were analyzed using Cox regression models to predict the length of survival. They found that an increased level of depressive affect over time was associated with an increased risk of mortality, even when the analysis was controlled for medical parameters.[42] Boulware and colleagues generated similar results when they evaluated baseline and longitudinal data from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, a large cohort of incident patients starting dialysis.[47] They determined that levels of depressive affect, as measured by invalidated mood questions from the SF-36, at the beginning of the study were not associated with increased overall mortality. However, similar to Kimmel's findings, using several different time-dependent analyses, the investigators demonstrated that persistently higher levels of depressive affect over time were associated with the increased risk of death and cardiovascular events in both adjusted and unadjusted analyses.

There is also evidence that the repeated measurement of a depression diagnosis is more informative than a cross-sectional assessment. As discussed previously, patients with ESRD who were depressed at two diagnostic interviews, spaced 16 months apart, reported correlations with a lower quality of life and more reported health problems.[46] Although the limited study duration prevented these results from being extended directly to mortality, it appears clear that a persistent course of depression represents an increased risk to the morbidity and mortality of patients with ESRD treated with HD. Hedayati and colleagues[88] recently reported on time to death or hospitalization in an ESRD sample. They found a hazard ratio of about 2 for patients with ESRD with depression when compared to patients with ESRD without depression.

Marital Issues

Depressed patients with ESRD may be at particular risk for marital difficulty.[89] In addition to the typical strain that the development of a chronic illness places on a couple,[90] the depressed patient could feel more easily overwhelmed and can be perceived as not being invested in the relationship. Role changes can be profound[29,91] because spouses can now become caregivers or wage earners, and this may promote further depression or resentment. There have been only a few studies that assess marital relationships in patients with ESRD, with one study reporting that greater than 50% of couples that included a patient with ESRD experienced marital discord.[84] Marital support and conflict may also be associated with the degree to which a patient adheres to the dialysis prescription.[71,84]

COMORBIDITIES OF DEPRESSION

Depression often presents with other common coexistent psychiatric conditions. It is important to carefully evaluate each presenting patient for the cooccurrence of these other conditions.

Substance Use

All patients with ESRD should be carefully screened for substance abuse because of the potentially nephrotoxic effects of some illicit drugs.[92] Additionally, patients with depression are often at a loss regarding how to effectively cope with their mood and may turn to drugs or alcohol to "self-medicate." One study found that in a sample of 145 HD patients, 28% were judged to have a problem with chronic alcohol abuse.[93] The study further found that the alcoholic group had poorer nutritional markers than the nonalcoholics. Little is known about the effect of intravenous drug use on dialysis or vascular access; however, active substance abuse should be considered an acute situation, and coordination of care with addiction specialists should be undertaken.

Anxiety Disorders

Anxiety has been demonstrated to be a complicating comorbid diagnosis for many medical problems[94,95] and often cooccurs with depression in ESRD populations.[45,46] It is consistently ranked as a major cause of years lost to disability in the United States.[96] There is relatively little anxiety research specific to patients with ESRD, but it appears that an anxiety diagnosis exerts a powerful negative effect on quality of life.[97,98] There is some suggestion that compound depression and anxiety might represent a clinical entity that has a synergistic effect on the quality of life.[97] One must consider that anxious patients can have characteristics on a spectrum from the more classic worried and withdrawn to agitated or angry. When disruptive behavior presents in patients with ESRD, it is important to try to understand the cause of the patient's distress and to explore whether stress and anxiety are leading to undesirable outcomes. Similarly, excessive anxiety might lead to somatic vigilance, a discomfort with changes in bodily sensations. This may be particularly important to evaluate in patients who often prematurely end their dialysis session because pain or discomfort might be a concomitant of anxiety.

Dementia/Delirium

Neurocognitive disorders are common in patients with ESRD.[99] Depression can be a precipitant for neurocognitive decline, and the evaluation of any patient who reports a change in his or her mental acuity should include a screen for depression. Withdrawal from dialysis is relatively common, especially in elderly patients or patients who fail to thrive,[100,101] and the physician should try to determine the patient's wishes, through an advanced directive, before the patient's mood and mental status may compromise his or her ability to provide a meaningful directive.[102]

TREATMENT OF DEPRESSION

The difficulties in identifying and assessing depression should not serve as barriers to the successful treatment of depression. Although there has been relatively little clinical

research on the treatment of depression in patients with CKD, the literature that does exist has been encouraging. The main treatment options for depression include psychotherapy and pharmacotherapy.

Psychotherapeutic Options

There are several forms of psychotherapies (cognitive-behavioral, interpersonal, supportive, group therapy) that have demonstrated consistent and substantial efficacy in the treatment of depression in general populations, which may well be effective tools for patients with ESRD as well.[103] In comparison to pharmacological interventions, psychotherapy has the advantage of few deleterious side effects, frequently introducing benefits such as improved sleep, improved interpersonal relationships, and improved regimen compliance. However, a significant disadvantage is that therapy typically requires the patient to be motivated to change. The first step in wanting to change is acknowledging the presence of a problem. Denial, an unconscious mental operation that allows the person to avoid facing harsh realities, is a considerable obstacle. Incorporating a mental health evaluation as a standard of care is one strategy to reduce barriers to psychological care and to minimize patients' resistance to psychotherapeutic interventions. Additionally, referring clinicians should explain their biopsychosocial[7] conceptualization of disease and how treating psychological components is essential for good medical care. There is little evidence on psychotherapeutic intervention in HD populations,[60,104] but the emerging literature is positive.[105,106] There is significant literature indicating that psychosocial interventions, such as cognitive behavioral therapy, are effective for treating mental health difficulties in a variety of medically ill populations.[107]

Pharmacotherapy

In today's healthcare environment, nephrologists have, in many ways, become primary care providers for patients with ESRD and often find themselves prescribing medications usually prescribed in primary care or other settings. When considering a psychotropic medication for patients with ESRD, it is important for nephrologists to balance their familiarity with the pharmacokinetics of psychotropic agents against the probability of the patient accepting a psychiatric referral, attending the appointment, and following through on the recommendations. Nephrologists must be aware of whether a drug is cleared through renal or hepatic metabolism, and whether the drug clearance is affected by HD or peritoneal dialysis (PD). Most psychotropic medications are protein-bound, lipid soluble, penetrate the blood–brain barrier, and are cleared by the liver, with the notable exception of lithium. Protein binding may be impaired in ESRD, which can affect drug metabolism.[108] Therefore, to reduce the potential for overdosing, consideration should be given to the reduction of the initial dose of psychotropic medications in this patient population. Clinical responses should be carefully monitored as doses are increased, and levels should be obtained if available.

Antidepressants have a potentially essential role in treating depression in patients with ESRD, with selective serotonin reuptake inhibitors (SSRIs) being the first line of pharmacological treatment.[109] Tricyclic antidepressants (TCAs) and SSRIs are typically cleared by the liver and therefore require only a minimal dose adjustment in patients without liver disease. For patients with ESRD, the initial dose of an SSRI is often half to two thirds of the usual dose. Typically, treatment with SSRIs should be continued for at least 4 to 6 weeks before deciding whether there has been a therapeutic benefit. If improvement is not achieved after 3 to 4 months, then consideration should be given to switching to another antidepressant as appropriate. Establishing an appropriate antidepressant regimen may involve trial and error. The nephrologist and patient should expect that adjustments will need to be made to identify the optimal medication and dosing.

There is some evidence that SSRIs are effective in the treatment of depression in patients with ESRD. An early study found a treatment advantage in 12 depressed patients with ESRD treated with the SSRI, fluoxetine over those given a placebo.[110] Wuerth and colleagues found that depressive symptoms were markedly ameliorated in PD patients who completed a 12-week course of treatment with sertraline, bupropion, or nefazodone, despite low rates of compliance overall.[111,112] Researchers in Korea found that fluoxetine significantly reduced HAM-D scores in patients with ESRD.[113]

For a variety of reasons, SSRIs are the preferred medication for the treatment of CKD patients with depression. SSRIs typically cause fewer anticholinergic symptoms than TCAs, are not associated with cardiac conduction abnormalities, and are less lethal in large doses, as compared to TCAs, which are lethal in large doses and can be used in suicide attempts. An additional benefit of SSRIs in this patient population is that they may reduce postural hypotension through effects on vascular tone.[114] Fluoxetine, the first available SSRI, is the best studied drug in this family.[108,109] Other medications in this family include paroxetine, sertraline, and citalopram.

Venlafaxine and bupropion hydrochloride are examples of a different class of antidepressants called selective norepinephrine reuptake inhibitors (SNRIs). The SNRIs should be used with caution in patients with ESRD because these drugs are primarily cleared by the kidney.[108] Bupropion has active metabolites that are almost completely excreted through the kidney. These may accumulate in dialysis patients, predisposing them to developing seizures. Monoamine oxidase inhibitors (MAOs) have numerous side effects and should be avoided if possible in patients with ESRD because of their potential to cause hypotension. All medications carry with them the risk of adverse effects and patients' regimens need to be carefully selected and then closely monitored. If the nephrologist does not believe that the regimen is sufficiently improving the depression, or he or she is not comfortable with the multiple iterations that are often required in gaining efficacy from antidepressants, a psychiatric consultation is warranted.

CASE PRESENTATION

A 63-year-old African American man with diabetes recently transferred into a HD center. He was employed as a bus driver and approaching retirement, and, after 6 months on

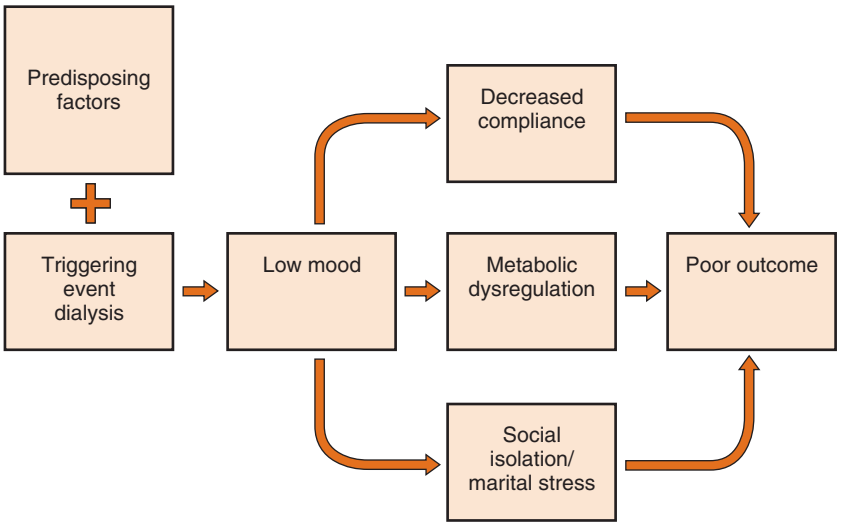


FIGURE 16-1 Proposed map of interaction between depression and ESRD.

dialysis, he had to stop working because of a disability. The patient was married to his second wife, who was many years younger. The majority of his friends and social interactions were centered at his job with the Transit Authority.

The nutritionist was concerned over the change in the patient's dietary compliance and excessive interdialytic weight gain. The patient dismissed the dietician's attempts at intervention, and a psychological consult was obtained. The psychologist found that the patient had been functioning quite well before stopping work, and then a chain of events transpired that developed into a vicious circle, promoting greater depression and poorer health (Figure 16-1). The patient confided that, since he began dialysis, he had been experiencing erectile difficulty. This, coupled with his stopping work, had him feeling like he was "less of a man." He began avoiding conversations with his wife during the day and sleeping alongside her at night. He also was less social with his friends at work.

The psychologist proposed an intervention that included family sessions to promote open communication, a referral to discuss the use of sildenafil, and "behavioral activation," a series of exercises designed to enable the patient to reengage in pleasurable activities despite his lack of desire. Simultaneously, the patient's beliefs about what it means to "be a man" were challenged. After some time, he was able to redefine his role from being a "provider" to that of a "partner." After 6 months of treatment, the patient was enjoying a modified lifestyle with his wife and friends that provided them with satisfaction and fulfillment. The patient's medication and diet compliance improved.

SUMMARY OF DEPRESSION IN CHRONIC KIDNEY DISEASE

Depression has a multifaceted etiology that can interact with the substantial burden of ESRD. The true prevalence rates for depression are difficult to establish because of the overlap of depressive and uremic symptoms. Using a clinician-administered, semistructured interview, the rates for a diagnosis of depression appear to be 20%–30%, depending on the patient population. High levels of depressive affect are more prevalent with studies reporting levels as high as 40%. Depression should not be measured cross-sectionally because longitudinal assessment has revealed a stronger association with outcome. A depression's deleterious effects may extend to higher rates of suicide, poorer nutrition, poorer treatment compliance, and decreased social support. It is also possible that depression is associated with changes in immunological or inflammatory responses. Depression may cooccur with substance abuse, anxiety disorders, or dementia, which complicate the treatment. The literature on treatment of depression in the setting of ESRD is still developing, but both psychotherapy and psychopharmacological strategies appear to be efficacious. SSRIs are typically the first line of medication treatment, and the initial dose for patients with ESRD is often half to two thirds of the usual dose.

Part II
Neurocognitive Function in Chronic Kidney Disease Etiology of Neurocognitive Impairment

The assessment of neurocognitive functioning is a vital part of the comprehensive care of the patient with CKD[115] because it can correlate with disease progression[116] and the likelihood of adherence to the medical regimen,[117] or it can serve as a gross measure of adjustment.[118] Tables 16-3 and 16-4 provide lists of cognitive domains and tests (respectively) that are used in the evaluation of cognition. Cognitive impairment is defined as a reduced function in at least two or more cognitive domains.[99] Impairment can range from subtle, with only minor impairment in a circumscribed domain, to gross diffuse dysfunction. The term *"dementia"* is used when there is a decline in cognitive functioning across multiple areas, including memory.[119] If the cognitive decline is transient and abrupt, the impairment is referred to as *"delirium."* Delirium may occur with concurrent dementia.[120] The most common type of dementia is Alzheimer disease. Alzheimer disease can be progressive and, in advanced stages,

TABLE 16-3 Cognitive Domains Evaluated by Neurocognitive Testing

INTELLIGENCE	OVERALL INTELLECTUAL FUNCTIONING INVOLVING COMPONENTS OF VERBAL AND PERFORMANCE SKILLS
Full scale IQ (FSIQ)	
Verbal scale IQ (VIQ)	
Performance scale IQ (PIQ)	
ATTENTION	
• Sustained attention	Attention for an extended duration of time
• Divided attention	Attention to multiple tasks or multiple task components
• Alternating attention	Ability to shift attention on tasks
• Memory • Short-term (working memory)	Retaining information for a relatively short duration of time
• Long-term	Retaining information for a longer duration of time
• Episodic	Recall of past personal events, autobiographical memory
• Semantic	Recall of information regarding factual world events, learned information
• Executive functioning	Cognitive functions involving goal-directed behavior, organization, planning
• Processing speed	A measure of speed in which a person performs intake and output of information

TABLE 16-4 Frequently Used Neurocognitive Tests to Assess Cognitive Functioning

Neuropsychological test	Cognitive abilities measured
Wechsler Adult Intelligence Scale (WAIS-III)	Intellectual functioning comprising verbal and performance domains
Wechsler Intelligence Scale for Children (WISC-IV)	Intellectual functioning comprising verbal, performance, memory, and processing speed domains
Wechsler Memory Scale (WMS-III)	Verbal memory, visual memory, attention
California Verbal Learning Test (CVLT)	Verbal memory, immediate and delayed recall
Trail Making Test, Forms A and B	Psychomotor speed, attention, visual scanning, and planning skills
Mini-Mental State Examination (MMSE)	Overall cognitive function, including attention, orientation, attention, language, and memory
The Modified Mini-Mental State (3MS)	Overall cognitive function, including attention, orientation, language, and memory
The Symbol Digit Modalities Test (SDMT)	Immediate visual memory, learning, hand-eye coordination, and reading-writing ability
The Controlled Oral Word Association Test (COWAT)	Verbal fluency, planning and organization, and semantic memory
Rey Auditory Verbal Learning Test (RAVLT)	Verbal learning, immediate memory, and retrieval from long-term storage
Conners' Continuous Performance Test (CPT)	Attention, processing speed, and psychomotor ability
Wisconsin Card Sorting Task	Attention and executive functioning (mental flexibility)
Cognitive Abilities Test (CAT)	Processing speed, memory, and stimulus discrimination
Paced Auditory Serial Addition Test (PASAT)	Attention, processing speed, and working memory
Stroop Color-Word Test	Selective and focused attention
Rey-Osterrieth Complex Figure	Memory, attention, and visuospatial ability

result in profound memory impairment.[121] Another common cause of dementia is vascular dementia, which is often characterized by a significant impairment in executive functioning.[115]

Manifestations of cognitive dysfunction may include difficulties within the domains of behavior, cognition, emotionality, or executive functioning.[122] Dysfunction in these areas may result from difficulty with memory, receptive and perceptual functions, communicating information, difficulty organizing information, motivational and attention difficulties, personality changes, and a decrease in goal-directed behavior.[123] Cognitive dysfunction may be a result of various factors. Certain amounts of cognitive dysfunction are associated with normal aging. Traumatic brain injury and stroke are two common causes of dysfunction. Viral and bacterial infections also cause cognitive impairment. Cognitive dysfunction has been associated with the progression of the acquired immunodeficiency syndrome (AIDS)[124] and Lyme disease.[125] Toxic exposure to alcohol or environmental fuels has also been associated with cognitive dysfunction.[120] Malnutrition, such as folic acid or vitamin B_{12} or C deficiency, may also alter neurocognitive functioning.[120] Additionally, hypothyroidism has been associated with cognitive impairment.[126,127]

Various consequences of kidney failure can contribute to cognitive dysfunction. HD patients are often older and are therefore at greater risk for cognitive difficulties.[128] Uremia has a significant impact on cognitive ability, with symptoms such as fatigue, nausea, drowsiness, irritability, decreased libido, and sleep disturbances[129–132] associated with reduced concentration, memory impairment, and intellectual functioning.[120,133–136] Anemia is another risk factor for compromised cognitive functioning in patients with kidney disease.[137] Reduced oxygen availability secondary to anemia may decrease cognitive function, especially in patients with other forms of neurological or cerebrovascular diseases.[116,138]

Treatment of anemia with recombinant human erythropoietin (rHuEPO) for 3 months improved cognitive functioning in patients with kidney failure.[139] Cognitive assessments were administered at three intervals: before erythropoietin treatment and after 3 and 12 months of treatment. Subjects completed each assessment approximately 24 hours after dialysis. After 3 months of treatment, patients showed improvement on the Symbol Digit Modalities Test (SDMT). This test requires learning, memory, psychomotor speed, and scanning efficiency skills. After 12 months of treatment, the Trail Making Test Part B also showed significant improvement in the patients. Temple and colleagues[140] assessed cognitive changes in 18 HD patients, 9 who were treated with rHuEPO and 9 controls. There was a significant, 8.7-point increase in WAIS-R IQ scores in the group that received rHuEPO treatment, compared to a nonsignificant change of 2.5 IQ points in the group that did not receive rHuEPO treatment. Singh and colleagues evaluated the impact of rHuEPO treatment on

cognitive status using P300 event related potentials (ERPs) as a marker of cognitive dysfunction.[141] Thirty anemic patients with CKD, 15 of whom were on HD and 15 patients with less severe kidney failure, were examined. All 30 patients received rHuEPO treatment and were compared to a control group of 30 healthy individuals who did not receive rHuEPO treatment. The authors found a reduction in P300 latency in both groups that underwent rHuEPO treatment and a significant increase in the P300 amplitude in the HD group, both markers of increased cognitive function. The control group did not demonstrate any significant change in ERPs.[141]

Psychological factors, such as depression, have also been found to affect cognitive functioning.[142] Depression has been found to impact memory.[142,143] Depression is highly prevalent among patients with CKD and therefore may contribute to the observed neurocognitive impairment. Tyrell and colleagues[144] assessed cognitive functioning and depression in a sample of older dialysis patients. Depression was assessed by their doctors and measured by the Montgomery-Asberg Depression Rating Scale (MADRS). Forty-five percent of patients were both depressed and cognitively impaired, as measured by the Mini-Mental State Examination (MMSE).[144] Pliskin and colleagues[134] tested whether cognitive functioning was associated with depression, as measured by the BDI. Results indicated significant differences in cognitive functioning when comparing a depressed group (mean BDI = 18.4) to a nondepressed group (mean BDI = 6.1). Specifically, those who were less depressed had higher full scale and verbal IQ scores.[134]

Other common comorbid disorders associated with kidney disease may also contribute to the development of cognitive impairment. Hypertension and diabetes have been associated with compromised cognitive ability. Hypertension has been found to be a risk factor for developing vascular dementia and Alzheimer disease.[120] This is hypothesized to be the result of the effect of elevated blood pressure on compromising the vasculature of cerebral white matter and promoting atherosclerosis.[120] Obisesan and colleagues[145] reported hypertension to be negatively associated with cognitive functioning, as measured by the MMSE. Hanon and colleagues[146] studied the impact of the antihypertensive medication, Eprosartan, on cognitive functioning in hypertensive patients across 28 countries. Antihypertensive treatment was associated with significant improvement in cognitive functioning as measured by MMSE after 6 months of drug treatment. Interestingly, the largest effect was found among the elderly.[146] The extent to which different antihypertensive medications are effective is an important area for further study.

Diabetes has also been associated with impairment in cognitive functioning. It is estimated that 45% of ESRD cases in the United States are to the result of diabetes.[147] Individuals with diabetes are at increased risk for cardiovascular and cerebrovascular disease.[148] Saczynski and colleagues reported that processing speed was reduced among individuals with diabetes compared to normoglycemic subjects. Additionally, patients with at least 15 years since diabetes diagnosis were found to be significantly more cognitively impaired than subjects more recently diagnosed with diabetes.[148] Arvanitakis and colleagues reported that diabetes mellitus was associated with decreased semantic memory and perceptual speed.[149] Furthermore, Sinclair and colleagues found that those with lower MMSE scores, and thus lower cognitive functioning, were less involved with self management of their diabetes than individuals who scored higher on the MMSE.[150] These findings highlight the possible impact that cognitive functioning may have on the adherence to medical regimens.

EPIDEMIOLOGY OF NEUROCOGNITIVE IMPAIRMENT

The rate of cognitive decline and its relationship to CKD are not well-delineated. Kurella and colleagues[151] assessed cognitive functioning in a sample of 80 patients with CKD not requiring dialysis and 80 patients with ESRD receiving HD. An association between stage of CKD and degree of cognitive impairment was found on the Modified Mini-Mental State (3MS), Trailmaking, and the California Verbal Learning Trial (CVLT). Seliger and colleagues reported that participants with moderate CKD were 37% more likely to develop dementia over a median of 6 years.[152]

It is unclear whether the HD procedure modifies cognitive functioning in patients with ESRD. Hemodynamic shifts resulting from dialysis treatment may cause short-term cognitive fluctuations[133] because changes in blood volume may cause cerebral edema and reduce intracerebral blood pressure and blood flow.[116] It is also possible that as dialysis treats uremia, there is a commensurate improvement in cognitive processing. One study identified such improvement in cognitive functioning 24 hours after HD.[153] Lewis and colleagues reported an increase in reaction time and visual-motor speed and accuracy 24 hours after receiving dialysis treatment.[154] Najafi and colleagues used the Conners' Continuous Performance Test (CPT) to assess attention and reaction time and did not find any changes in these variables before and after HD treatment in 45 HD patients.[155] Williams and colleagues measured cognitive functioning, specifically attention and memory, at 1 hour, 24 hours, and then 67 hours after HD treatment, and found that subjects performed significantly more poorly at 67 hours postdialysis compared to the earlier measurements.[133] These studies suggest that HD can have various effects on cognitive performance, and neurocognitive performance may differ depending on the timing of the assessment.

Studies that have examined differences in cognitive functioning between HD and PD patients have demonstrated inconsistent results.[151] Yount and colleagues reported that those receiving PD had a greater attention ability than those receiving HD.[156] Wolcott and colleagues also reported better cognitive functioning among PD patients when compared to those receiving HD.[157] In contrast, Rozeman and colleagues[158] did not find any significant differences in cognitive functioning when comparing patients treated with the two modalities.

The differing neurocognitive performance between HD and PD groups may, in part, be the result of patient selection or intrinsic differences in the treatment modalities.[137] HD is typically performed three times a week and can create abrupt hemodynamic shifts. Additionally, there is also a gradual accumulation of uremic toxins and fluid between treatments. In contrast, PD provides a more stable control of uremia and electrolytes because of its continuous nature.[159] There also

may be some inherent differences in baseline cognitive functioning in patients who choose one treatment method over the other, or other unmeasured differences in characteristics.

PREVALENCE OF NEUROCOGNITIVE IMPAIRMENT

The number of incident cases of ESRD has been steadily increasing in the United States.[147] It has been estimated that the prevalence of cognitive impairment in patients with stage 5 CKD is 30%–60%.[128] For example, Sehgal and colleagues concluded that 22% of HD patients evidenced mild cognitive impairment (MMSE 18 to 23), and 8% had more severe impairment (MMSE 0 to 17).[160] Fazekas and colleagues examined cognitive functioning in 30 HD patients and 30 matched controls. Sixty percent of the HD patients evidenced cognitive impairment as measured by DSM-III criteria for the diagnosis of dementia or deficits, according to neuropsychological testing.[161] Additionally, MMSE scores were significantly different between the two groups, with HD patients demonstrating cognitive impairment. Another study[151] compared the prevalence of cognitive impairment in 80 patients to CKD and 80 patients with ESRD. In the combined sample, 17% evidenced global cognitive impairment. Twenty-seven percent of patients with ESRD demonstrated global cognitive impairment, whereas 15% of CKD patients evidenced impairment. Interestingly, only patients with advanced stage CKD demonstrated impairment.[151] Murray and colleagues assessed cognitive functioning in 338 HD patients. Based on their cognitive test battery results, patients were divided into mild, moderate, or severe impairment groups, with 14% categorized as having mild impairment, 36% moderate dysfunction, and 37.3% with severe impairment.[133] Overall, there is evidence that cognitive dysfunction is common in patients with ESRD and that the stage of CKD may be an important determinant. However, the specific cognitive domains that are affected by CKD are less clear.

Intellectual Functioning

The findings have been mixed when intellectual functioning is measured in patients with CKD.[162] Earlier studies are hard to evaluate because the amount and frequency of dialysis provided are often not reported. Dialysis administration may significantly affect cognitive results.[134] Furthermore, many studies did not consider cognitive assessments relative to the time of dialysis.[163]

Pliskin and colleagues[134] administered a neuropsychological test battery to 16 patients with ESRD receiving dialysis and 12 age- and education-matched controls from other medical clinics. Testing was conducted on a day-after-dialysis treatment. Intelligence was assessed using the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The full scale intelligence quotient (FSIQ) did not significantly differ between the two groups, with a mean of 84 in both groups. Similarly, there were no differences between groups on the verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ). The authors then divided the sample by the median BDI score (median = 13.5) to form two groups, one clinically depressed with a mean BDI score of 18.4 and one nondepressed group (mean BDI = 6.1). Interestingly, the depressed group scored significantly lower on the FSIQ and VIQ compared to the nondepressed group.[134] Williams and colleagues[133] administered a neuropsychological test battery to 20 HD and 10 PD patients. Intelligence testing, as measured by the Kaufman Brief Intelligence Test (K-Bit), was completed 24 hours after dialysis treatment. There were no significant differences between the HD and PD groups in intellectual functioning. Additionally, both groups fell within the average range of functioning.[133]

Bawden and colleagues[164] assessed cognitive functioning among children with ESRD. All participants were either currently receiving dialysis treatment or waiting to begin dialysis. Testing was administered to 22 patients with ESRD and 22 sibling controls of the children with ESRD. Intelligence was assessed with the Wechsler Intelligence Scale for Children (WISC-III). Children with ESRD scored in the low-average range on the FSIQ, PIQ, and VIQ, whereas the sibling controls were in the average range in these three domains. Furthermore, the two groups differed significantly on the FSIQ, VIQ, and PIQ. Overall, children with ESRD demonstrated lower intelligence scores compared to their siblings.[164] Duquette and colleagues[165] examined intellectual functioning in 30 children with CKD. Fifteen participants were active dialysis patients, and 15 participants received other forms of treatment. The CKD group was matched with 41 control participants. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI). The two groups differed significantly on the FSIQ, VIQ, and PIQ, with the control group performing better than the CKD group. Additionally, the CKD group had a significantly higher percentage of individuals with FSIQ scores below the 25th percentile.[165]

Memory

Similar to intellectual functioning, the results of studies evaluating associations between CKD and memory functioning have been inconsistent. In one study[164] memory functioning was assessed using the Wide Range Assessment of Memory and Learning Test and the Nonverbal Selective Reminding Test. Children were tested on immediate recall for sentences and visual stimuli. They were also tested on wordlist recall and recall of the location of targets in a visual presentation. There were no significant differences on any of these memory tasks between the children with ESRD and their matched sibling controls.[164] Similarly, Pliskin and colleagues assessed immediate and delayed memory function in patients with ESRD and age, gender, education, and race matched medical controls recruited from general medical and rheumatology clinics using the Wechsler Memory Scale (WMS) and found no significant differences between the two groups on memory tasks.[134]

The impact of kidney transplantation on memory has also been of interest. Mendley and Zelko[166] studied nine children with ESRD before kidney transplantation and 1 year after a successful transplant. Memory was assessed using the Paced Auditory Serial Addition Test (PASAT) and the Children's Paced Auditory Serial Addition Test (CHIPASAT). Memory was measured by the ability to add a series of numbers from memory. There was a significant improvement in working

memory after a successful kidney transplant. These results must be interpreted with caution, however, because the PASAT and CHIPASAT not only measure one's ability to remember numbers, but also the ability to perform arithmetic. Because there was no control group also being tested over time, it is possible that the improvement could have been to the result of improvement in arithmetic skills and repeated test-taking.[166] Another study assessed the impact of kidney transplantation on neurocognitive function using a within group study design.[167] Twenty-eight adult patients with ESRD were assessed before and 6 months after kidney transplantation. Using the Rey Auditory Verbal Learning Test (RAVLT), they demonstrated an increase in verbal and nonverbal memory performance after transplantation while controlling for depression. Participants recalled more words on the test after transplantation than before.[167]

The impact of dialysis treatment on memory function has also been studied. Williams and colleagues[133] compared memory function of HD patients to PD patients at 1, 24, and 67 hours after dialysis treatment. As hours increased after dialysis, the HD group performed worse on immediate recall and delayed recall auditory memory, with the overall performance worst at the 67 hour postdialysis assessment. The HD group recalled fewer words from a list at each consecutive time point for both immediate and delayed recall compared to the PD group. Although memory progressively worsened for this group, performance on recall did not decrease for the PD sample over time. When compared to a normative group with equivalent gender, age, and intellectual functioning, HD had similar memory scores at the initial assessment, 1 hour after dialysis. At the 24-hour time point, the HD group's recall was reduced to 1 standard deviation below the normative sample, and, by the 67-hour time point, they fell 2 standard deviations below the mean for recall.[133] Griva and colleagues[153] also compared memory in a sample of HD and PD patients. This study demonstrated a significant improvement in verbal and visual memory, as measured by the RAVLT and SDMT, in the HD patients after receiving treatment. Additionally, a reduction in urea levels was associated with better memory in this sample.[153]

Attention and Processing Speed

The long-term impact of nocturnal daily hemodialysis (NHD) on attention, reaction time, and psychomotor speed has been investigated. Jassal and colleagues[168] examined cognitive functioning in patients treated with NHD at a baseline assessment and after an average of 8.3 months. Patients showed significant improvement in processing speed and attention, as measured by Trail Making Test (TMT) Parts A and B.[168]

Mendley and Zelko demonstrated improvement in processing speed, as measured by the Cognitive Abilities Tests (CATs), and reaction time, as measured by the Conners CPT, in children when values after kidney transplantation were compared to the assessment before transplantation.[166] Umans and colleagues found decreased performance on the Stroop Word and Stroop Color Reading tests, demonstrating worse attention and processing speed in ESRD patients relative to age and education-matched controls recruited from medical clinics.[169] A study[156] that evaluated 554 ESRD patients compared attention in HD patients, PD patients, and CKD patients not yet receiving dialysis treatment. Participants who received PD or no dialysis treatment demonstrated better focused attention than those who received HD treatment. Focused attention is one's ability to perform a task with little distraction and was assessed using the Stroop Color-Word test, Trailmaking Test B, Digit Symbol task, and Digit Span-forward task. Education, vocabulary score (as measured by the WAIS-III), age, race, creatinine level, and type of therapy were all significant predictors of focused attention, explaining 30% of the variance in a regression model. When controlling for demographic variables, however, serum creatinine emerged as the only meaningful predictor of the variance in focused attention.[156]

While some studies have found significant impairment in attention and processing speed in CKD patients, results are inconsistent. Umans and Pliskin[169] administered neuropsychological tests assessing attention and processing speed to 10 stable HD patients and 10 control subjects without kidney disease. There were no differences in attention and processing speed between these two groups on a variety of measures, including the Stroop Color-Word Test, the Trailmaking Tests A and B, Digit Span taken from the WAIS-R, the PASAT, and the CPT. While some studies have found there to be deficits in these areas, the authors reported that well dialyzed ESRD patients may not evidence impaired attention and processing speed.[169]

NEUROCOGNITIVE FUNCTIONING FOLLOWING TRANSPLANTATION

Cognitive changes following kidney transplantation have also been the subject of scientific inquiry. Kramer and colleagues[170] assessed neurocognitive functioning in HD patients before and after kidney transplantation. These patients were compared to healthy control subjects. Cognitive functioning was measured using evoked potentials, the MMSE, and the Trailmaking Test. Before transplantation, evoked potentials of the dialysis patients were significantly delayed and smaller in amplitude compared to healthy subjects. Additionally, before transplantation, dialysis patients performed significantly more poorly on the two neuropsychological tests compared to healthy subjects. Following transplantation, dialysis patients did not differ on the MMSE or Trailmaking Test when compared to healthy subjects. However, latency between evoked potentials decreased and amplitude of evoked potentials increased, suggesting an improvement in cognitive functioning.[170] Mendley and Zelko[166] assessed neuropsychological functioning in children with ESRD before and after kidney transplantation. There were significant improvements after transplantation in processing speed, as measured by the CAT; discriminatory ability, using the Connors' CPT; and working memory, as measured by the PASAT or the CHIPASAT. Other cognitive functions assessed did not differ before and after transplantation.[166] A study in which participants were assessed on cognitive domains before transplantation and 6 months after transplant also demonstrated an increase in memory performance.[167] Psychomotor performance and attention, however, did not significantly improve after transplantation.[167] Mendley and Zelko[166] also found improvement in memory functioning following kidney transplantation.

The impact of immunosuppressive medications on cognitive functioning following kidney transplantation is also of interest. Long-term glucocorticoid use has been associated with hippocampal atrophy, an area of the brain associated with memory.[171] Using the 15 Words Test, one study demonstrated impairment in long-term memory, more specifically delayed memory recall, in 50 kidney transplant patients taking immunosuppressive medication.[171] Immunosuppressive medications have also been associated with various side effects, including tremors, weakness, seizures, and difficulty with sleep.[163] Contemporary kidney transplant recipients, however, often do not experience these symptoms, possibly as a result of efforts to minimize immunosuppressive therapy.[163] Furthermore, cognitive impairment related to glucocorticoid treatment may improve by reducing dosages or steroid-free immunosuppressive regimens.[163,171]

SEQUELAE OF NEUROCOGNITIVE IMPAIRMENT

Impairment in cognitive functioning in those with kidney disease may affect levels of compliance with dialysis treatment, medication adherence, and fluid and dietary restrictions.[67,117] Rates for nonadherence to the dialysis prescription range from 30%–60%.[67,172] Nonadherence to the medical regimen has been associated with increased mortality.[66,67] Additionally, nonadherence to immunosuppressive medication in kidney transplantation is a primary cause of rejection,[173] with one metaanalysis finding that nonadherent transplant patients are seven times more likely to have graft failure than those who were adherent.[174]

One study sought to examine the association between cognitive impairment and levels of adherence in 63 older adults receiving HD treatment. Cognitive impairment was assessed using the 3MS, with a score below 80 marking impairment. Approximately 39% of the sample was found to have cognitive impairment. Of those with cognitive impairment, 58% were found to be nonadherent, as measured by serum phosphate levels.[117] A limitation of this study was that it focused on adherence in those who were cognitively impaired and did not measure adherence in those who were cognitively intact.

Cognitive deficits involving attention, memory, processing speed, and other functions may compromise the understanding of medical procedures and treatment regimens.[67,122] Expectations that patients with CKD are able to manage the complex demands of their medical management may not be realistic, especially given the common occurrence of cognitive impairment in this population. Addressing cognitive impairment is critically important for overall adjustment to chronic illness and prognosis in CKD. Quality of life and wellbeing may be favorably influenced if cognitive ability can be maintained.

TREATMENT OF NEUROCOGNITIVE IMPAIRMENT

Despite the high prevalence of cognitive impairment in CKD, studies that describe intervention methods for this population are not available. However, there are several strategies that have been used in other populations with chronic illness, which may be applicable to patients with CKD. For example, computer-based strategies have been used to improve attention, memory, and executive functioning.[175] One group used computer retraining to increase attention in a group of patients with multiple sclerosis.[176] Other cognitive rehabilitation strategies are compensatory in nature such as using calendars and logs for recording activities such as taking medications or dietary regimens. These techniques are often useful for individuals with memory impairment. Breaking tasks into smaller parts may help decrease inattention and reduce overwhelmed feelings. Involving the patient's supportive network in managing activities of daily living is another helpful strategy to use. Neurological rehabilitation is a field still in its infancy, but it holds much promise, especially for those with less severe impairment.

Compromised cognitive functioning in patients with CKD often goes undetected.[117] Routine screening of cognitive function should be a component of regular care for the patient with ESRD. An efficient way to monitor cognitive function is to regularly test gross neurocognitive performance using a simple tool, such as the MMSE. Patients can be referred for further assessment if a substantial change in function occurs.

CASE EXAMPLE

A 60-year-old HD patient was diagnosed with ESRD 5 years ago. She had a long-standing history of hypertension and was compliant with dietary, medication, and clinic attendance goals. Recently, however, there was an increase in the variability of the patient's blood pressure. She admitted to having difficulty remembering to take her medications. Her nephrologist requested neuropsychological testing, which included the MMSE, sections of the WMS, and Trailmaking Test. She obtained a score of 22 on the MMSE, indicating obvious cognitive impairment. Specifically, the patient had difficulty recalling new information (verbal and nonverbal) and with control of attention. She performed considerably worse on working memory and immediate memory scales and demonstrated compromised processing speed and attention relative to her overall neurocognitive performance. Neurological examination, imaging of the brain, and biochemical assessments revealed no apparent reason for her impairments other than ESRD.

Compensatory strategies were identified to help her better manage her medical regimen. She was advised to use external cues, such as an alarm watch, to alert her when to take her medications. Her family was encouraged to assist the patient by placing her medications into a week-long pill case. A food diary log was also suggested to help her record her food intake more specifically and monitor her diet. It was also recommended to the patient's healthcare team that they relay information to her in a simple and slow-paced manner to accommodate her impaired information processing ability. Verbal information should also be supplemented by simple, legible written instructions. Within a few weeks the patient was more regularly taking her medication, and her diet improved. She appreciated the extra help and felt less overwhelmed by her medical problems. The patient's neurocognitive deficits may have been related to aging, vascular

complications, or uremia. Regardless of the etiology, her neurocognitive deficits were addressed by basic behavioral strategies that allowed her to regain some of the lost functions.

SUMMARY OF NEUROCOGNITIVE FUNCTION IN CHRONIC KIDNEY DISEASE

The possible etiologies of impaired neurocognitive functioning in CKD patients include aging, vascular disease, diabetes, uremia, anemia, depression, toxic exposure, and malnutrition. The impact of hemodynamic changes on acute neurocognitive processing is still unclear. The prevalence of impairment ranges from 30% to 80%, depending on assessment methodology and population factors. Deficits appear in global intellectual functioning, memory, attention, and processing speed. It appears that neurocognitive function improves mildly following transplantation. Cognitive impairment may negatively affect treatment compliance. There are scarce data on treatment strategies for cognitive impairment in CKD patients.

A full list of references are available at www.expertconsult.com.

Chapter 17

THE PEDIATRIC PATIENT WITH CHRONIC KIDNEY DISEASE

Bradley A. Warady, M.D. and Vimal Chadha, M.D.

Although uncommon in children, chronic kidney disease (CKD) can be a devastating disorder with the potential for serious long-term ramifications. Reference to CKD includes the spectrum of disease ranging from mild kidney damage with normal solute clearance to end-stage renal disease (ESRD). Despite some basic similarities with the clinical manifestations seen in adults, CKD in childhood is, in fact, characterized by many unique features not experienced by the adult population. For instance, growth and cognitive development are two of the major characteristics of childhood, and, unlike adults who have completed their physiological and intellectual maturation, infants and young children are in the formative phase of their neurodevelopment and physical growth, both of which may be adversely affected by CKD. This is especially pertinent because a substantial percentage of the pediatric CKD population develops impaired kidney function very early in life as a result of congenital or inherited disorders (*vide infra*). Additional CKD-related complications, such as renal osteodystrophy/metabolic bone disorder, poor nutrition, anemia, and cardiovascular disease (CVD), are also characterized by features unique to the pediatric population. Most significant is that early recognition and intervention provide the greatest opportunity to decrease the CKD-related morbidity and mortality and possibly even slow the progressive loss of kidney function.[1] This chapter, in turn, is designed to highlight the identification and treatment of clinical issues that frequently develop in children with CKD (or chronic renal insufficiency [CRI]), as defined by a creatinine clearance <75 ml/min/1.73 m^2, irrespective of the primary kidney disorder. Although these same issues were addressed in the prior edition of this book, the authors have made every effort to incorporate the most noteworthy information on the topic that has emerged subsequently to the earlier publication.

DIAGNOSIS AND EVALUATION OF CHRONIC KIDNEY DISEASE

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) has developed a CKD classification schema for patients >2 years of age that is designed to improve consistency when discussing the severity of kidney injury and to help target diagnostic and treatment initiatives.[2] The diagnosis of CKD is established based on the presence of structural or functional kidney damage and the level of kidney function (estimated glomerular filtration rate [GFR]), irrespective of the specific type of underlying kidney disorder/diagnosis. The classification is based on five stages, with higher stages (e.g., stage 5) representing lower levels of GFR. In the pediatric literature and as noted previously, CRI has historically been defined by a creatinine clearance <75 ml/min/1.73 m^2, a value that falls within stage 2 CKD. The rationale for including individuals with a higher GFR within the CKD population is that substantial kidney damage often occurs before the GFR declines, and these individuals are also at increased risk for adverse outcomes associated with CKD.

Although the level of GFR has been recommended as the primary criterion for defining and staging CKD, an important caveat should be recognized when using these definitions in young children. In the pediatric population, the normal level of GFR varies according to age, gender, and body size. Whereas the normal GFR in young adults is ~120 to 130 ml/min/1.73 m^2, the normal value is much lower than this in early infancy, even when corrected for body surface area. It subsequently increases along with the increase in body size for up to 2 years.[3] The normal range of GFRs at different ages is given in Table 17-1.[3,4]

TABLE 17-1 Normal GFR in Children and Adolescents

AGE (SEX)	MEAN GFR ± SD (ml/min/1.73 m²)
1 wk (males and females)	41 ± 15
2-8 wk (males and females)	66 ± 25
>8 wk (males and females)	96 ± 22
2-12 y (males and females)	133 ± 27
13-21 y (males)	140 ± 30
13-21 y (females)	126 ± 22

Although the GFR can be measured by inulin or iohexol clearance,[5] the determination of creatinine clearance in a 24-hour urine collection is a more commonly used clinical approach to measurement. Unfortunately, the accuracy of a 24-hour urine collection is often compromised by an incomplete collection; in addition, with progressive worsening of kidney function, creatinine clearance overestimates GFR because of an enhanced tubular secretion of creatinine.[6] Although the accuracy of the creatinine clearance can be increased by blocking the tubular secretion of creatinine by oral cimetidine,[7] this method of assessment is rarely used. Serum cystatin C has been extensively investigated as a potentially more accurate marker of kidney function than serum creatinine. Cystatin C has several advantages over creatinine such as lower intrapatient variability,[8] and its levels are inversely correlated with kidney function independent of age, gender, height, and body composition in patients over 2 years of age.[9] With the consistent use of immunonephelometry for measuring serum cystatin C levels, most of the studies comparing serum cystatin C to creatinine clearance have shown superiority or equivalence of cystatin C as a marker of GFR in children.[10]

For practical purposes, multiple prediction equations have been developed to estimate GFR.[11,12] The Schwartz formula, which was developed based on serum creatinine determinations using the Jaffe technique, has been the most widely used formula in pediatric practice. The GFR is calculated as follows:

$$C_{Cr}(\text{ml/min/1.73 m}^2) = 0.55 \times \text{Height (cm)}/S_{Cr}(\text{mg/dl})$$

(The constant is 0.45 for infants <1 year of age and 0.7 for adolescent boys)

Despite its ease of use, the Schwartz equation has become imprecise with the current use of the enzymatic method for creatinine estimation.[12] Investigators of the Chronic Kidney Disease in Children (CKiD) study, a prospective, multicenter initiative funded by the National Institutes of Health designed to follow the course of more than 560 children with CKD for 4–8 years,[13] have subsequently developed a more accurate GFR estimating equation based on the measurement of GFR derived from the plasma disappearance of iohexol in more than 500 children (1–16 years) with CKD, along with the determination of height, serum creatinine, serum cystatin C (assayed by the turbidimetric assay), blood urea nitrogen (BUN), and gender in these same patients. The resulting equation is as follows:

$$\text{Estimated GFR} = 39.1 \times (\text{Height (m)}/P_{cr})^{0.516} \times (1.8/\text{Cys C})^{0.294} \times (30/\text{BUN})^{0.169} \times (1.099^{\text{male}})(\text{Height (m)}/1.4)^{0.188}$$

A "bedside" version of the equation in which the enzymatically measured serum creatinine divided by height (cm) is multiplied by a constant 0.413 (irrespective of age or gender) provides a good approximation of the estimated GFR.[12]

DEMOGRAPHICS

Epidemiological information on the incidence and prevalence of pediatric CKD is currently limited, imprecise, and flawed by methodological differences between the various data sources. This is especially true for the earlier stages of CKD when patients are often asymptomatic but potentially more susceptible to therapeutic interventions aimed at changing the course of the disease and avoiding ESRD.[14] Most of the existing data on the epidemiology of CKD during childhood concentrates on the late and more severe stages of renal impairment and are not population-based in nature.[15] In addition, some methodologically well-designed childhood CKD registries are limited by being restricted to small reference populations.[16,17] Finally, direct comparisons of the incidence and prevalence rate of childhood CKD in different geographical areas around the world are difficult because of differences in study age group, characterization of the degree of renal insufficiency, and disease classification.

In the United States, a wealth of data on children with CKD is available from the registry of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) (*vide infra*), but unfortunately, it does not provide any information on incidence and prevalence rates.[18] Perhaps the most comprehensive data on pediatric CKD come from the ItalKid Project, a prospective population-based registry that includes all incident and prevalent cases of CKD (GFR <75 ml/min/1.73 m²) in children (<20 years) from throughout Italy.[19] This registry reported a mean CKD incidence of 12.1 cases per year per million of age-related population (MARP).

Unlike adults in whom the primary etiologies of CKD are diabetes and hypertension, the greatest percentage of pediatric CKD is secondary to congenital renal disorders such as obstructive uropathy and aplasia/hypoplasia/dysplasia. Out of the 7037 patients with CKD (GFR ≤75 ml/min/1.73 m²) reported in the 2008 annual NAPRTCS report, almost one-half of the cases are accounted for by patients with the diagnoses of obstructive uropathy (21%), aplasia/hypoplasia/dysplasia (17%), and reflux nephropathy (8%).[18] Whereas structural causes predominate in the younger patients, the incidence of glomerulonephritis increases in those older than 12 years. Among the individual glomerular causes, only focal segmental glomerulosclerosis (FSGS) accounts for a significant number of patients (8.7%), whereas all other glomerulonephritides combined contribute less than 10% of the causes of childhood CKD. For reasons that are not yet clear, FSGS is three times more common in blacks than in whites (18% vs. 6%).[18] Data from Italy have also revealed that hypoplasia with or without urological malformations accounts for as many as 57.6% of all cases of CKD.[19] Nonetheless, there are distinct geographic differences in the reported causes of CKD in children, in part, due to environmental, racial, genetic, and cultural (consanguinity) differences. Data from the Japanese National Registry reveal a very high proportion (34%) of cases secondary to glomerular diseases, primarily FSGS and immunoglobulin A (IgA) nephropathy.[20] Heritable causes of CKD, such as cystic kidney disease, primary

hyperoxaluria, cystinosis, Alport syndrome, and congenital nephrotic syndrome, reportedly represent a substantial percentage of the CKD cases in Jordan[21] and Iran[22] where consanguinity is more common. Many of the less-developed countries that continue to suffer from the burden of infectious diseases, such as hepatitis C, malaria, schistosomiasis, and tuberculosis, experience infection-related glomerulonephritis. Human-immunodeficiency virus (HIV) associated nephropathy, which causes ESRD in only a small number of children in the United States,[23] is likely an underreported cause of nephropathy in children because an increasing incidence of pediatric HIV is evident in the underdeveloped regions of South America, Africa, and Asia, where data on pediatric CKD are poorly collected or nonexistent.

GROWTH FAILURE

Growth failure is one of the most onerous and visible clinical manifestations of CKD in children, and patients often fail to achieve a final adult height consistent with either population norms or their own genetic potential. According to the NAPRTCS registry, more than one-third of children with CKD are less than the 3rd percentile (standard deviation score [SDS] of −1.88) for height upon entrance to the registry.[18] Although there is some correlation between the degree of renal insufficiency and growth impairment, significant growth failure can be seen at all levels of kidney function because 18% of the subjects in the 2008 NAPRTCS registry with an estimated clearance ≥60 ml/min/1.73 m^2 had a height SDS worse than −1.88. Overall, patients with CKD are nearly 1.44 SD below age and sex specific norms for height, whereas the youngest patients (0–1 years) are the most severely growth retarded portion of the population with a mean height SDS of −2.34 at baseline.[18] This is an important issue because one-third of postnatal statural growth is attained during the first 2 years of life, and any insult to growth that occurs during this time may have a profound impact on final adult height. Finally, pubertal growth is also often adversely affected in the setting of CKD. The onset of puberty is delayed by an average of 2.5 years, the duration of the pubertal growth spurt is 1.6 years shorter in duration than normal, and the height gain experienced during puberty is only approximately 50% of that experienced by normal children.[24]

In addition to its negative influence on the achievement of a normal final adult height and the potential association between poor growth and health-related quality of life,[25] poor incremental growth in association with CKD has been associated with an increased risk of morbidity and mortality in children.[26] Furth and colleagues, using data from the NAPRTCS, demonstrated that children with significant growth failure, as reflected by a height SDS more negative than −2.5 at the time of dialysis initiation (and thus reflective of care provided during the period of CKD), had a significantly increased risk of hospitalization and a twofold higher risk of death compared to patients with better growth (height SDS >−2.5).[27] In a similar manner, analysis of data from the U.S. Renal Data System (USRDS) on 1112 subjects <17 years of age revealed that growth failure was associated with a more complicated clinical course and an increased risk of death for children on dialysis.[28] The more severely growth retarded patients also had more hospital days per month of dialysis and were less likely to attend school full-time.[28] Although review of these study results is not intended to suggest that poor growth is the immediate cause of poor patient outcomes, growth retardation may possibly serve as a surrogate for the clinical severity of the disorder and/or for the provision of suboptimal clinical care. Therefore, delineation of the optimal management of growth retardation in children with CKD may be crucial to the establishment of clinical treatment standards, which may, in turn, reduce the burden of hospitalization and mortality in these patients.

Although multiple factors such as protein-energy malnutrition, acidosis, extensive salt, and water losses and secondary hyperparathyroidism, may contribute to growth failure, perturbations of the growth hormone/insulin like growth factor (GH/IGF) axis are the predominant factors contributing to the impaired growth associated with CKD, particularly in those patients outside the period of infancy.[29–32] Normally, growth hormone (GH) released from the pituitary gland is stimulated by growth hormone releasing hormone (GHRH) from the hypothalamus. The GH is bound by GH receptors within the liver with the subsequent production of IGF-1. The majority of IGF-1 is bound to acid labile subunit and insulin growth factor binding protein 3 (IGFBP-3) in a ternary complex, and a portion of the remaining free (bioactive) IGF-1 stimulates cartilaginous growth in bone.[33] In patients with CKD, there is an increased pulsatile release of GH from the pituitary gland due to a less active negative feedback loop to the hypothalamus. In addition, the metabolic clearance rate of GH is reduced, resulting in a rise in the circulating GH concentration. However, despite the presence of the elevated GH concentration, GH receptor downregulation within the liver and defects in postreceptor signal transduction result in decreased IGF-1 synthesis by the liver.[34,35] Furthermore, the bioavailability of IGF-1 is reduced as a result of elevated concentrations of the IGF binding proteins (IGFBP). Increased circulating levels of IGFBP-1 and -2 are inversely correlated with residual GFR and height[36] and probably contribute directly to the resistance to the anabolic and growth promoting effects of GH and IGF-1.[37] Thus renal failure is not a state of GH or IGF-1 deficiency but instead a state in which the regulation and bioavailability of components of the GH/IGF/IGFBP system are altered.

Recognition that recombinant human GH (rhGH) treatment improves the height velocity of children with CKD has dramatically changed the therapeutic approach available to correct/prevent the growth retardation associated with renal insufficiency.[24,38–43] According to the recently published K/DOQI Clinical Practice Guideline for Nutrition in Children with CKD,[39] rhGH therapy should be considered in children with CKD stages 2 to 5 and 5D with short stature (height SDS <−1.88), and the potential for linear growth if growth failure (height velocity-for-age SDS <−1.88) persists beyond 3 months despite treatment of nutritional deficiencies and metabolic abnormalities, as discussed under the section on Nutritional Issues (*vide infra*). The recommended rhGH dose to be given daily is 0.05 mg/kg given by subcutaneous injection. It is noteworthy that treatment with rhGH is most effective when prescribed to those with CKD, before the need for dialysis, and a better response has been shown to be associated with younger age

(prepubertal) at therapy initiation, the degree of bone age retardation, the extent of height SDS gain during the first year of therapy, and renal dysplasia as the primary disease etiology.[40–44] Furthermore, the target height deficit at the initiation of therapy and the duration of treatment are the most important predictors of cumulative height gain.[43] While the most dramatic response to rhGH therapy occurs during the first year of treatment followed by a progressively reduced effect thereafter, with sustained use of rhGH many patients achieve a final height within the normal range.[24,42,43,45]

Historically, there has been a concern that the acceleration of growth that results from rhGH treatment during the prepubertal years might be offset by an earlier onset and/or shorter duration of pubertal growth. However, long-term follow-up results from the German Study Group for Growth Hormone Treatment in Chronic Renal Failure has revealed that the onset of the pubertal growth spurt was actually delayed in boys treated with rhGH (although not in girls), and the duration of the growth spurt was no different from controls.[24] Although the prepubertal bone maturation was slightly accelerated in children treated with rhGH, the rhGH induced prepubertal growth stimulation was sufficient to override this effect.[24] Most significant was the finding that those patients with CKD who received rhGH grew significantly better than those patients who did not, and only the former group of patients had a normal mean final adult height. In an additional study of note, Hokken-Koelega and colleagues found that rhGH treatment during puberty was associated with a sustained improvement in height SDS without deleterious effects on GFR and bone maturation.[46]

Before initiating rhGH therapy, patients should be evaluated for preexisting or worsening osteodystrophy radiographically and by checking a serum PTH level. Baseline hip x-rays should be obtained due to the theoretical increased risk of slipped capital femoral epiphysis and avascular necrosis of the femoral head associated with rhGH therapy. Any limp and/or hip or knee pain should be carefully evaluated. An ophthalmological evaluation should also take place at baseline because of the reported but rare treatment-related complication of pseudotumor cerebri. Despite this level of caution, recent database evaluations have revealed an excellent safety profile of rhGH therapy in children with CKD.[40,47]

Finally, the height velocity of patients receiving rhGH should be closely monitored, with the weight related dose modified every 3–4 months to maintain the standard dosing regimen. Typically, rhGH is discontinued when the child has closed epiphysis, has achieved his or her target height percentile, or when adverse events such as severe hyperparathyroidism, pseudotumor cerebri, active neoplasia, or slipped capital femoral epiphysis occur. If discontinued for reasons other than closed epiphysis, reinstitution of rhGH should be considered if the height velocity significantly decreases and the reason for discontinuing the drug has resolved. A simple approach to the use of rhGH is provided in Figure 17-1.[48]

Remarkably, despite these results, a substantial percentage of growth-impaired children with CKD do not receive treatment. According to the 2008 NAPRTCS report, rhGH utilization in eligible (e.g., growth retarded) children with CKD was 11.1% at baseline and increased to only 22.1% by the end of 1 year.[18] A recent multicenter study examining obstacles to rhGH use in children with CKD revealed that although psychosocial reasons (family refusal or noncompliance) were cited as a likely cause in 30% of patients, there was no identifiable reason precluding rhGH usage in 25% of the patients.[49] These findings suggest the need for additional education of patients and health care providers.

NEUROCOGNITIVE DEVELOPMENT

The majority of brain growth occurs during the first 2 years of life, when it is most likely to be vulnerable to nutritional deficiencies and metabolic insults. The impact of the uremic milieu on brain development during this critical period and the ensuing cognitive development of infants and children with CKD is an area of study that has, until recently, received little attention with little discrimination between those with ESRD and those with earlier stages of CKD.[50] This is all the more interesting, given the long-term and significant clinical manifestations that abnormalities of cognition may have on patient outcome. A seminal report on the developmental outcome of children with CKD during infancy demonstrated a high prevalence of mental dysfunction, microcephaly, hypotonia, dyskinesia, and seizures.[51] With subsequent recognition of the crucial role played by aluminum exposure and malnutrition, more favorable developmental outcomes have been reported by using aggressive means to prevent and treat malnutrition (often with the use of supplemental tube feeding) and by avoiding aluminum-containing compounds.[52–54] Nonetheless, there continues to be evidence that neurological functioning and development are adversely affected by the uremic state because children with CKD have significantly lower IQ scores when compared to their sibling controls.[55] The severity of CKD may also influence the developmental outcome, as Hulstijn-Dirkmaat and colleagues reported a higher mean developmental index in 15 toddlers with predialysis CKD as compared to that of 16 children who were receiving dialysis therapy.[56] From these reports and other published literature, it appears that, overall, at least 25% of infants and toddlers who have severe renal insufficiency will exhibit developmental delay, whereas the impact of milder forms of CKD on the neurodevelopment of infants is unknown.

There is also evidence that with good nutritional support and optimal medical management, many of these children will show improvement over time.[57] Warady and colleagues[52] found that of 19 former infants with severe CKD and on peritoneal dialysis (PD) who were retested at >4 years of age (mean age: 6.6 ± 1.3 years), 15 (79%) had a normal IQ, although only 72% and 56% of these patients scored in the average range on tests of verbal and nonverbal functioning, respectively. Almost all of these patients had been transplanted, and of the 16 school-aged patients, 15 (94%) were attending school as full-time students in an age-appropriate classroom.[52] More recently, Madden and colleagues reported on the cognitive and psychosocial outcome of 16 infants who began dialysis during the first year of life. When retested at a mean age of 5.8 years, two-thirds (67%) of them had IQ scores within the average range, whereas 87% were within at least two SD of normal (mean IQ = 86.6).[58] It is likely that some of this improvement in neurocognitive function

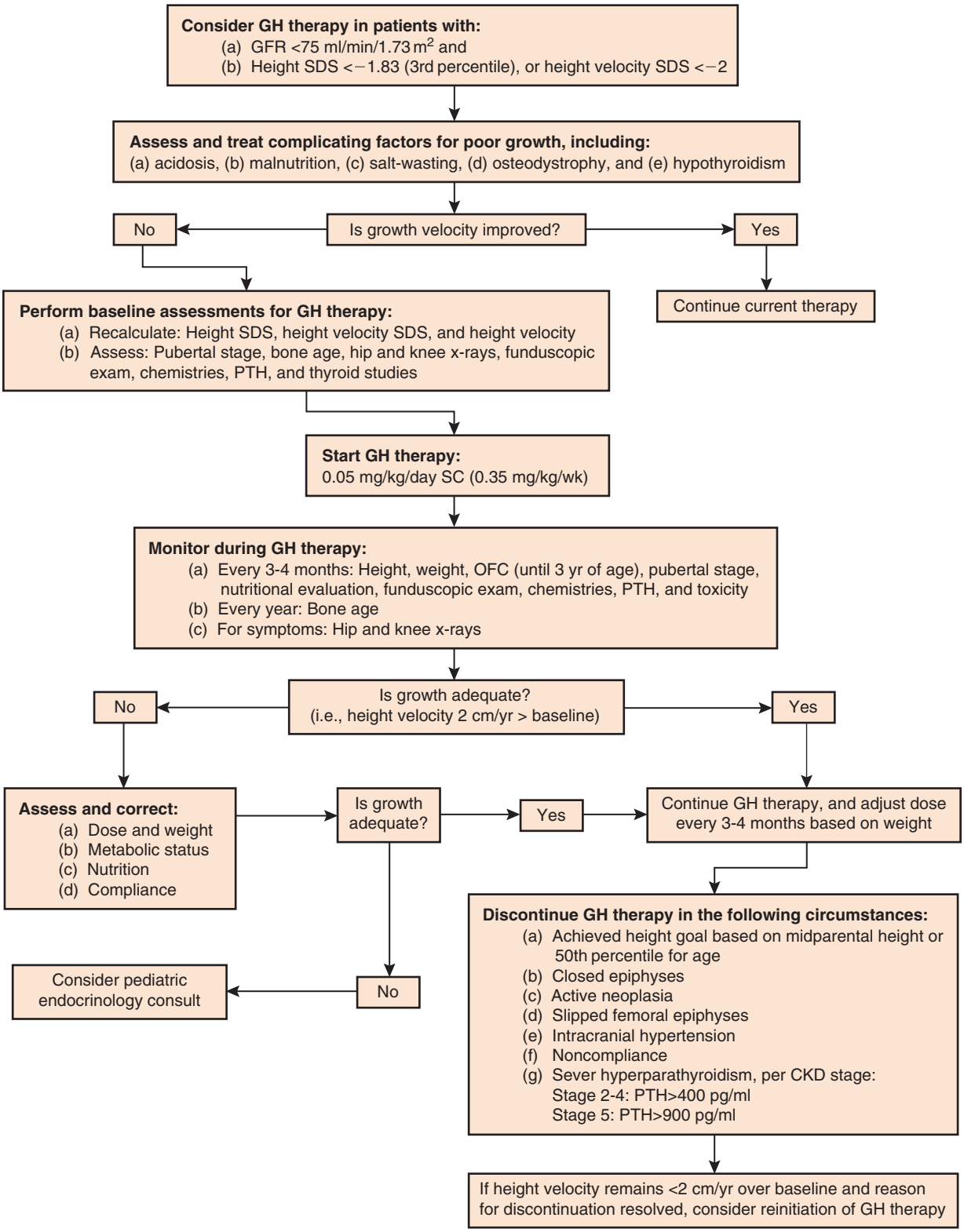


FIGURE 17-1 Management of GH therapy.

is related to kidney transplantation as Lawry and colleagues found that the mean IQ of the transplanted population was higher than those who remained on dialysis.[59]

Finally, studies conducted on specific aspects of development in children with CKD have found verbal performance and memory skills to be significantly affected, leading to substantial impairment of school functioning. Fennell and colleagues found that children with CKD had deficits in verbal abstraction abilities and that verbal performance progressively worsened with a greater duration of kidney

failure. In addition, children with CKD exhibited deficits in visual-motor abilities and had poorer sustained attention skills compared to matched controls.[60] Gipson and colleagues evaluated 20 children and adolescents and controls and found that the patients with CKD were deficient in their initiation and sustaining behaviors within the executive function domain, even when controlling for IQ and chronologic age, and had significantly lower memory abilities than controls, especially short-term verbal memory, short-term visual memory, and new learning capacity.[61] When cognition is impaired, academic functioning may prove suboptimal with particular reference to skills in reading, writing, and mathematics, findings that emphasize the necessity of early screening for deficits with a standardized battery of neurocognitive assessments and aggressive intervention when deficits are detected.[62–64]

Nutritional Issues

Protein energy malnutrition (PEM) is a common problem in patients with CKD and is one of the major contributors to the poor growth seen in these patients, especially during the first few years of life. However, due to the growing epidemic of obesity, there is also an increasing concern about overnutrition and its long-term implications in patients with CKD. Accordingly, regular evaluation of nutritional status and the provision of optimal nutrition are key components in the overall management of children with CKD. The goal of nutritional therapy is to achieve normal patterns of growth and body composition by an intake of appropriate amounts and types of nutrients and avoidance of metabolic abnormalities.

The origin of malnutrition in children with CKD is multifactorial (Table 17-2); however, an inadequate voluntary dietary intake is considered a major contributing factor, especially in infants. Nausea and vomiting are common in infants and children with CKD, with delayed gastric emptying and gastroesophageal reflux being detected in as many as 73% of patients with these problems.[65] Medical management with antiemetic medications (metoclopramide, domperidone) and antacids (H-2 blockers, proton-pump inhibitors) or surgical intervention (Nissen fundoplication) is frequently required. Additionally, whey predominant formulas can be used in these patients, based on the ability of the formulas to stimulate gastric emptying.[66] Adolescents are the other patient group who appear to be particularly vulnerable to malnutrition due to their poor eating habits. They skip meals, favor fast foods, and in the presence of imposed dietary restrictions, find it difficult to meet the nutritional requirements of normal pubertal growth and development. They may benefit from individualized counseling and from having a special rapport with a renal dietitian.

TABLE 17-2 Causes of Protein-Energy Malnutrition (PEM) in Children with Chronic Kidney Disease

Inadequate food intake secondary to:
Anorexia
Altered taste sensation
Nausea/vomiting
Emotional distress
Intercurrent illness
Unpalatable prescribed diets
Impaired ability to procure food because of socioeconomic situation
Chronic inflammatory state
Catabolic response to superimposed illnesses
Possible accumulation of endogenously formed uremic toxins and/or the ingestion of exogenous toxins
Removal of nutrients during dialysis procedure
Endocrine causes such as:
Resistance to the actions of insulin and IGF-I
Hyperglucagonemia
Hyperparathyroidism

Assessment of the nutritional status of children with CKD requires the evaluation of multiple indices because there is no single measure that by itself can accurately assess a patient's nutritional status. A variety of physical measurements and anthropometric assessments plotted on appropriate growth charts, along with the assessment of dietary intake, are required to give a complete picture. Several of the previously suggested assessments,[67,68] such as midarm anthropometry and serum albumin, are not recommended by the current K/DOQI Pediatric Nutrition Guidelines.[39] Triceps skinfold thickness (TSF) was considered to reflect total fat mass, and the combination of TSF and midarm circumference (MAC) were used to calculate the midarm muscle circumference (MAMC) and midarm muscle area (MAMA), which are presumed to reflect total muscle mass. These measures are no longer recommended as a part of routine assessment because skinfold thickness measurement is extremely operator-dependent and lacks precision.[69] In the presence of fluid overload, both MAC and TSF are likely to be overestimated.[70]

Serum albumin has been considered a useful index of nutritional status in the past,[68] and hypoalbuminemia has been consistently associated with increased mortality in both adults[71] and children with CKD.[72] However, important limitations have recently been identified with respect to the ability of the serum albumin level to function as a reliable marker of malnutrition in the setting of CKD.[70,73] Serum albumin is depressed in the setting of both systemic inflammation and volume overload,[74] and in the absence of inflammatory markers is not predictive of increased mortality.[75] Therefore, although the serum albumin value remains an important component of the general evaluation of children with CKD, its role as a marker of nutritional status is questionable.

The Subjective Global Assessment (SGA), a method of nutritional assessment using clinical judgment rather than objective measures, has been widely used to assess the nutritional status of adults with CKD. An SGA specific for the pediatric population has recently been developed and validated in children undergoing major surgery,[76] and its applicability in children with CKD is currently being studied.

Energy

In children with CKD, spontaneous energy intake decreases with deteriorating kidney function,[77] despite the absence of any evidence suggesting that the energy requirements of children with CKD differ from those of healthy children. Energy requirements for children with CKD should be considered to be 100% of the estimated energy requirement

(EER) for chronological age that is individually adjusted for the physical activity level (PAL) and body mass index (BMI).[39,78] While inadequate voluntary energy intake has been clearly demonstrated in infants with CKD,[79,80] energy intakes for older children are generally normal relative to their body size.[81] Because energy intake is the principle determinate of growth during infancy, malnutrition has the most marked negative effect on growth in children with congenital disorders leading to CKD.[82] In fact, only in infants has maximizing caloric intake to at least 80% of normal been noted to be an effective means of improving height velocity in association with CKD,[79,80,82] with a rare report of a similar experience in older children. In a study of 35 children younger than 5 years with CKD stages 4 to 5, significant weight gain and accelerated linear growth was demonstrated in those starting enteral feeding at <2 years of age, while improved weight gain and maintenance of growth velocity was observed in those starting enteral feeds at age 2 to 5 years, in each case without exceeding normal energy requirements.[79] However, if children younger than 3 years with a length (or height) for age <−1.88 SDS fail to achieve expected weight gain and growth when receiving the EER based on chronological age, estimated requirements may be increased by using height age related recommendations.

Supplemental nutritional support should be considered when the usual intake of a child with CKD fails to meet his or her energy requirements and the child is not achieving expected rates of weight gain and/or growth for age. Infants with CKD requiring fluid restriction or those who have a poor oral intake may require a greater caloric density of their milk formula than the standard 20 kcal/oz. Oral intake of an energy-dense diet and commercial nutritional supplements should be considered the preferred route for supplemental nutritional support; however, if poor appetite or vomiting preclude an adequate oral intake, the institution of tube feedings should be considered. Nasogastric (NG) tubes, gastrostomy catheters, gastrostomy buttons, and gastrojejunostomy tubes have all been used to provide supplemental enteral feeding to children with kidney disease with encouraging results. The feeding can be given as an intermittent bolus or more commonly by continuous infusion during the night.[48] Detailed recommendations regarding initiation and advancing tube feeds are available in the 2008 update of K/DOQI Clinical Practice Guidelines for Nutrition in Children with CKD.[39]

Nutritional therapy, irrespective of the route of administration or caloric density of the formula, should provide a balance of calories from carbohydrate and unsaturated fats within the physiological ranges recommended as the Acceptable Macronutrient Distribution Ranges (AMDR) of the Dietary Reference Intake (DRI). Recommended AMDR for children older than 4 years are 45%–65% from carbohydrate, 25%–35% from fat, and 10%–30% from protein; children younger than 3 years need a somewhat greater proportion of fat (30%–40%) in their diets to meet energy needs.

Protein

Low-protein diets reduce the generation of nitrogenous wastes and inorganic ions that might be responsible for many of the clinical and metabolic disturbances characteristic of uremia. In addition, there is a nearly linear relationship between protein and phosphorus intake,[83] which results in the frequent association between hyperphosphatemia and a high-protein diet.[84] Accordingly, low-protein diets decrease the development of hyperphosphatemia, metabolic acidosis, hyperkalemia, and other electrolyte disorders. A large number of clinical trials and experimental studies have examined the impact of dietary protein restriction on the rate of progression to ESRD in adults.[85–88] In the Modification of Diet in Renal Disease (MDRD) trial, no significant beneficial effect of decreasing Dietary Protein Intake (DPI) from 1.3 to either 0.58 or 0.3 g/kg/d, supplemented with essential keto acids, could be demonstrated, while subtle signs of a suboptimal nutritional status were noted with these diets.[89]

Pediatricians, on the other hand, are rightly concerned about the potential for harmful effects of severe dietary protein restriction, particularly as it pertains to the growth of infants and young children with CKD. Experimental studies in young animals have shown that a decrease in dietary protein intake during the normally rapid period of growth to a level that is sufficient to slow the deterioration of kidney function, does adversely affect growth.[90] As a result, very few studies of dietary protein restriction have been conducted in children with CKD.[91,92] In one such study, Uauy and colleagues reported on the poor growth of infants with CKD who were prescribed a modest protein restricted diet during the feasibility phase of a multicenter trial.[91] In the largest and most significant pediatric trial, 191 children with CKD stages 3 to 4 were randomized to a reduced dietary protein intake aiming at 100% of the Recommended Dietary Allowance (RDA) (0.8 to 1.1 g/kg ideal body weight [defined as the weight at the same percentile as the child's height percentile for the same age and sex]) or to continue ad libitum intake (mean intake 181% of RDA). This modest reduction in protein intake, with the maintenance of energy intake greater than 80% of the RDA in both groups, did not adversely affect growth, serum albumin, or the rate of CKD progression within the observation period of 2–3 years.[92] Hence, although there is no evidence for a nephroprotective effect of dietary protein restriction, protein intake can be restricted safely to 0.8 to 1.1 g/kg/d in children with CKD.

While the spontaneous dietary protein intake is reduced in progressive CKD in a manner similar to that of energy intake, the energy intake tends to be critically low (<80%–85% of RDA), whereas the DPI is typically far in excess of the average requirements, ranging from 150% to 200% of the RDA.[81,92,93] Current K/DOQI Pediatric Nutrition Guidelines recommend maintaining dietary protein intake at 100% to 140% of the DRI for ideal body weight in children with CKD stage 3 and at 100% to 120% of the DRI in children with CKD stages 4 to 5 (Table 17-3).[39] As in adults, the "restriction" of protein intake is recommended as a means of decreasing the dietary phosphorus intake and the risk for hyperphosphatemia because of the frequent occurrence of CVD in children with CKD (*vide infra*). It is advised that at least 50% of the total protein intake consist of protein of high biological value such as the protein from milk, eggs, meat, fish, and poultry. Protein requirements may be increased in patients with proteinuria and during recovery from intercurrent illness and may be adjusted to height age instead of chronological age if evidence of protein deficiency exists.

TABLE 17-3 Recommended Dietary Protein Intake in Children with CKD Stages 3 to 5

AGE	DRI (g/kg/d)	RECOMMENDED FOR CKD STAGE 3 (g/kg/d) (100%-140% DRI)	RECOMMENDED FOR CKD STAGES 4-5 (g/kg/d) (100%-120% DRI)
0-6 mo	1.5	1.5-2.1	1.5-1.8
7-12 mo	1.2	1.2-1.7	1.2-1.5
1-3 y	1.05	1.05-1.5	1.05-1.25
4-13 y	0.95	0.95-1.35	0.95-1.15
14-18 y	0.85	0.85-1.2	0.85-1.05

(Adapted from National Kidney Foundation, KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update, Am. J. Kidney Dis. 53 [Suppl. 2] [2009] S1-S124.)

Lipids

Dyslipidemia is a frequently recognized complication of CKD in children,[94] occurs relatively early in the course of CKD (i.e., stage 3 CKD), and increases in prevalence with decreasing kidney function.[2] Hypercholesterolemia and hypertriglyceridemia have been reported in 69% and 90% of children with CKD stage 5, respectively. The dyslipidemia seen in children with CKD has complex underlying metabolic alterations and is characterized by increased levels of serum triglycerides in combination with high levels of VLDL and intermediate-density lipoproteins (IDLs), low levels of HDL particles, and normal or modestly increased levels of total and low density lipoprotein (LDL) cholesterol.[94–96] This pattern of dyslipidemia has been labeled "*atherogenic*." In addition, hypertriglyceridemia has been shown to be an independent contributor to the development of CVD[97,98] and may also accelerate the progression of CKD.[99]

The optimal management of dyslipidemia in children with CKD is not clearly defined. Treatment of malnutrition related to impaired kidney function is essential and should supersede any potential rise in lipid levels that might result from it. On the contrary, prevention and treatment of obesity in patients with CKD is an important strategy to reduce the risk of hyperlipidemia.[100] Correction of metabolic acidosis, vitamin D therapy, and correction of anemia with erythropoietin each also seem to have some normalizing effect on dyslipidemia in children with CKD.[101–103] The K/DOQI Dyslipidemia Guidelines' recommendations,[104] endorsed by the K/DOQI Cardiovascular Guidelines,[105] recommend that the dietary and lifestyle recommendations made for adults are also appropriate for postpubertal children and adolescents with CKD. Prepubertal children should follow recommendations from the National Cholesterol Expert Panel in Children and Adolescents (NCEP-C).[106] A consensus statement on dietary recommendations for children and adolescents, recently published from the American Heart Association (AHA)[107] and endorsed by the American Academy of Pediatrics (AAP), provides more current guidance than the NCEP-C recommendations for children and adolescents with CKD. The latter publication recommends that if the serum LDL cholesterol is >100 mg/dl, less than 30% of calories should come from dietary fat, of which <7% should be from saturated fatty acids, and the daily cholesterol intake should be <200 mg. For serum triglyceride >150 mg/dl, therapeutic lifestyle changes (TLC) are recommended along with a low-fat diet and a low intake of simple carbohydrates. The child should be encouraged to ingest complex carbohydrates in lieu of simple sugars and concentrated sweets and to use unsaturated fats such as oils and margarines from corn, safflower, and soy. Plant stanol esters in the form of dietary supplements reduce intestinal cholesterol absorption and may provide a safe and effective means of reducing serum cholesterol.

Lipid-lowering drugs such as statins may be used judiciously in selected patients, such as in adolescents with stage 5 CKD if LDL cholesterol is ≥160 mg/dl or in those with a LDL cholesterol <130 mg/dl but a combination of a fasting triglyceride level ≥200 mg/dl and a non-HDL cholesterol (total cholesterol minus HDL) of ≥160 mg/dl. Statin therapy should also be considered for those whose LDL cholesterol remains above 130 mg/dl after an adequate (6 months) trial of TLC.[104] Efficacy and safety of statin therapy has been shown in short-term studies; however, additional data on long-term safety, especially with respect to growth and nutrition, are needed before statins can be recommended for use in children of all ages.[104] Fish oil has been shown to reduce hypertriglyceridemia in a small group of children with ESRD,[108] and there are reports of statin usage in children with nephrotic syndrome.[109] Nevertheless, at this time there is insufficient evidence to support the regular long-term usage of the standard lipid-lowering therapies such as statins and fibrates in children of all ages, despite their frequent usage in adults.

Acid-Base and Electrolytes

Fluid and electrolyte requirements of individual children with CKD vary according to their primary kidney disease and the degree of residual kidney function. Infants and children normally have a relatively larger endogenous hydrogen ion load (2–3 mEq/kg) than do adults (1 mEq/kg); in turn, metabolic acidosis is a common manifestation of CKD in children and an important negative influence on growth through a number of growth-factor-specific mechanisms, including reduction in thyroid hormone levels and blunting of IGF response to rhGH.[110] Furthermore, studies performed in adults and children have shown that chronic acidosis is associated with increased oxidation of branched-chain amino acids, increased protein degradation,[111] and decreased albumin synthesis.[112] Persistent acidosis also has detrimental effects on bone because it alters the normal accretion of hydroxyapatite into bone matrix and causes bone demineralization as bone buffers are increasingly used for neutralizing the excess acid load. Thus it is recommended that the serum bicarbonate level should be maintained at or above 22 mEq/L by supplementing with oral bicarbonate as needed.[39]

Whereas in healthy people the body's sodium balance is maintained by alterations in urinary sodium excretion, sodium requirements in children with CKD are dependent on the underlying kidney disease and the degree of renal insufficiency. Children who have CKD as a result of obstructive uropathy or renal dysplasia are most often polyuric and may experience substantial urinary sodium losses despite advanced degrees of CKD. The growth of these children may be hampered if ongoing sodium and water losses are

not corrected. Fine and colleagues demonstrated poor weight gain in animals deprived of salt with a resultant decreased extracellular volume, bone mass, and fat mass.[113] The beneficial effect of sodium and water supplementation on the linear growth of 24 young children with CKD was subsequently reported.[30] In contrast, children with CKD resulting from a primary glomerular disease, or those who are oliguric or anuric, typically require a sodium and fluid restriction to minimize fluid gain, edema formation, and hypertension. The prescribed fluid intake is usually a fraction of the calculated maintenance volume adjusted for the degree of oliguria. According to the most recent 2005 Dietary Guidelines, the sodium intake for children older than 2 years should be restricted to <1,500 mg (65 mmol),[114] which corresponds to sodium intake of 1 to 2 mmol/kg/day for those younger than 2 years. These patients should be advised to avoid processed foods and snacks from fastfood restaurants as the majority (75%) of sodium in the diet comes from salt added during food processing. The sodium content of other food items should be checked carefully on food labels, and the sodium content of medications may need to be monitored.

Potassium homeostasis in children with CKD is usually unaffected until the GFR falls to <10% of normal. However, children with renal dysplasia, post-obstructive kidney damage, severe reflux nephropathy, and renal insufficiency secondary to interstitial nephritis often demonstrate renal tubular resistance to aldosterone and may manifest hyperkalemia, even when their GFR is relatively well-preserved. The hyperkalemia experienced by these children is exacerbated by volume contraction (and can be particularly common in salt losers), and the majority of the patients respond to salt and water repletion. In patients who are persistently hyperkalemic, dietary potassium intake should be limited. As potassium is infrequently listed on food labels and cannot be tasted, a list of foods rich in potassium such as chocolates, French fries, potato chips, bananas, green leafy vegetables, dried fruits, and orange juice should be provided to patients and their families. Altering the methods of food preparation, such as soaking vegetables before cooking, helps decrease potassium content. Moderate to severe hyperkalemia may require treatment with a potassium binder such as sodium polystyrene sulfonate (Kayexalate®); in hypertensive children, calcium polystyrene sulfonate can be used instead to decrease the sodium load. In the case of infants and young children being fed milk formula, the potassium content of the formula can be reduced by pretreating it with a potassium binder.[115] Attention should also be paid to medications such as potassium sparing diuretics, cyclosporin, and angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), all of which may cause or exacerbate hyperkalemia. If constipated, the patient should be treated aggressively as significant quantities of potassium are eliminated through the gastrointestinal route in patients with CKD.

Vitamins and Micronutrients

Vitamins and minerals are essential for normal growth and development, and either a deficiency or an excess can prove harmful. Unfortunately, the vitamin and mineral needs of pediatric patients with CKD are not clearly defined, other than for vitamin D, and the limited available data are derived from patients undergoing maintenance dialysis. Children with CKD are prone to develop vitamin deficiencies because of anorexia and dietary restrictions, and they are also at risk of developing toxic levels of vitamins when the renal clearance is significantly impaired.

The current K/DOQI Pediatric Nutrition Guidelines[39] recommend a dietary intake of at least 100% of the DRI for thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_8), cobalamin (B_{12}), ascorbic acid (C), retinol (A), α-tocopherol (E), vitamin K, folic acid, copper, and zinc for children with CKD stages 2 to 5, and suggest supplementation of vitamins and trace elements if dietary intake alone does not meet 100% of the DRI or if clinical evidence of a deficiency, possibly confirmed by low blood levels of the vitamin or trace element, is present.[39] Because most infant milk formulas, including Similac PM 60/40, are fortified with both water-soluble and fat-soluble vitamins, the majority of infants with CKD receive the DRI for all vitamins (including vitamin A) by dietary intake alone and do not require vitamin supplementation.

Carnitine

Carnitine is an essential compound in the oxidative process of fatty acids and adenosine triphosphate formation,[116] and the kidney is the major site for its synthesis in humans. Although there is documented evidence of carnitine deficiency in patients undergoing hemodialysis,[117] and far less information regarding its status in those receiving PD, there is little information on the carnitine status of children with CKD. Carnitine deficiency can result in the development of anemia, cardiomyopathy, and muscle weakness.[117] However, most (but not all) of the few pediatric studies that have been conducted on the subject of carnitine deficiency in dialysis patients have provided evidence for an increase in the plasma carnitine level after carnitine supplementation with no associated change in any symptoms.[118] Currently, there is insufficient evidence to support the routine use of carnitine in either the pediatric CKD or dialysis patient population.

Anemia

Anemia is a frequent complication of CKD both in children and adults,[119,120] and there is substantial evidence that it is an important predictor of patient morbidity and mortality.[121] The anemia of CKD is associated with a number of physiological abnormalities, including decreased tissue oxygen delivery, increased cardiac output, cardiac enlargement, ventricular hypertrophy, congestive heart failure,[122] decreased cognition and mental acuity,[123] impaired immune responsiveness,[124] and inferior quality of life.[125] Most notably, analysis of the NAPRTCS database also revealed that the presence of anemia (hematocrit <33%) 1 month after initiation of dialysis was associated with an increased risk for prolonged hospitalization and with an estimated 52% greater risk of death.[126] In a more recent NAPRTCS database analysis of more than 2500 children with predialysis CKD, anemic children (hematocrit <33%) were 55% more likely to be hospitalized when compared to nonanemic children (odds ratio 1.55).[127]

The prevalence of anemia increases with worsening stages of CKD.[127,128] In the previously mentioned NAPRTCS database analysis, Staples and colleagues found that the prevalence of anemia increased from 18.5% in CKD stage 2 to

68% in CKD stage 5.[127] Analysis of data from the CKiD study revealed that the hemoglobin (Hb) declined by 0.3 g/dl for every 5 ml/min/1.73 m^2 decrease in GFR below a GFR of 43 ml/min/1.73 m^2 as measured by iohexol disappearance (which is equivalent to a GFR of 58 ml/min/1.73 m^2 when estimated by the Schwartz formula), underscoring the fact that the decline in Hb starts during the early stages of CKD.[129] Therefore, all patients with CKD, regardless of the stage or underlying cause, should have their Hb checked at least annually.[130] It should, however, be noted that younger children often need more frequent laboratory monitoring because of expected changes in values that occur during growth.

In an effort to standardize the management of anemia in children with CKD, evaluation and treatment guidelines have been developed in both Europe and North America.[131] In North America, the latest K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease were updated in 2006 with an amendment published in 2007.[130,132] As per current recommendations, monitoring anemia by Hb level is preferred over hematocrit, because Hb is a stable analyte which is measured directly and is not influenced by differences in instrumentation, hyperglycemia, duration of sample storage, and storage temperature.[133]

Traditionally anemia in CKD has been defined as an Hb value of <11 g/dl. However, the recommended thresholds defining anemia have now been changed to reflect the variation that naturally occurs across the pediatric population. According to the latest K/DOQI guidelines, anemia in children with CKD is defined as a Hb concentration <5th percentile of normal for age and sex, which, unlike in adults, varies greatly. The NHANES III Study revealed that the 5th percentile for Hb may vary by as much as 2.8 g/dl from younger to older boys and by 2 g/dl for boys and girls of a similar age group.[134] The normative values used to define anemia in children older than 1 year are thus taken from NHANES III data, whereas the norms for infants younger than 1 year are derived from other previously compiled data.[135] Staples and colleagues observed that the prevalence of anemia in a cohort of more than 2,500 children with CKD stages 2 to 5 increased by 9% (from 35% to 44%), when anemia was defined based on age- and gender-specific Hb values as opposed to a fixed value of <11 g/dl, the lower limit recommended by K/DOQI.[127,132]

The pathophysiology of anemia in children with CKD is no different from that in adults, and the principal cause remains a decrease in the renal production of erythropoietin.[136] Additional factors that may cause or contribute to anemia include iron deficiency, shortened erythrocyte life span, hyperparathyroidism, acute and chronic inflammatory conditions, aluminum toxicity, folate and vitamin B_{12} deficiency, hypothyroidism, and hemoglobinopathies such as α-thalassemia.

The etiology of iron deficiency in children with CKD is multifactorial. Apart from low dietary intake of iron that may occur because of anorexia, children with CKD experience significant blood loss (~6ml/m^2 per day) in the gastrointestinal tract,[137] and from repeated phlebotomies necessary for laboratory tests. The iron status of CKD patients is commonly assessed by checking serum ferritin (only available blood marker of storage iron and an acute phase reactant), and transferrin saturation (TSAT), the latter calculated as the serum iron × 100 divided by the total iron binding capacity (TIBC) and which reflects the adequacy of iron available for erythropoiesis. Levels of serum ferritin >100 ng/ml and TSAT >20% are generally believed to reflect adequate iron stores.[130,138] However, functional iron deficiency, characterized by the presence of adequate iron stores as defined by conventional criteria but with the inability to sufficiently mobilize this iron to support erythropoiesis, is a well-recognized condition in CKD population. While functional iron deficiency typically responds to the provision of additional iron therapy, some CKD patients with a biochemical profile that is indistinguishable from functional iron deficiency fail to respond to supplemental iron and likely have an inflammatory iron block. New information is emerging on the complex relationship between inflammation and iron metabolism.[139] One chemical that has received a great deal of attention is hepcidin, a liver-derived peptide regulator of iron homeostasis that serves as a key mediator of hypoferremia in inflammatory states. Hepcidin levels are found to be elevated in the CKD population as inflammatory cytokines (IL-6) stimulate the hepatic release of hepcidin, and its clearance is decreased with declining GFR.[139] In addition, serum hepcidin levels show a strong correlation with serum ferritin in patients with anemia of inflammation. Based on animal and human studies, Nemeth and his colleagues have elucidated an important link between inflammatory cytokines, hepcidin, and iron metabolism, whereby IL-6 acts directly on hepatocytes to stimulate hepcidin production, which in turn acts as a negative regulator of intestinal iron absorption and macrophage iron release.[140]

The initial workup of anemia in children with CKD should include red blood cell indices (MCV, MCH, MCHC), reticulocyte count, white blood cell count with differential, platelet count, and iron parameters such as serum iron, total iron binding capacity (TIBC), and serum ferritin. The reticulocyte hemoglobin content (CHr), another test recommended in the adult guidelines for the assessment of iron adequacy for erythropoiesis, has not been well-studied in the pediatric CKD population.[141]

The treatment of CKD-associated anemia was revolutionized in 1986 with the introduction of recombinant human erythropoietin (rHuEPO) therapy.[138] In turn, the use of erythropoietic stimulating agents (ESA) such as erythropoietin-alfa, along with iron supplements continue to remain key elements of anemia management in patients with CKD. The average dosage of erythropoietin-alfa prescribed for children is 150–200 units/kg/wk given by the subcutaneous route, while younger patients (<1 year) frequently require higher doses of up to 350 units/kg/wk given in two to three doses. The requirement for higher doses in the youngest age group is likely due to increased clearance of rHuEPO in these patients, which has been speculated to be caused by the presence of nonhematopoietic binding sites for the erythropoietin molecule. There is a general tendency for the rHuEPO dose to decrease over time because lower doses are required for maintenance of the Hb level as opposed to the dose required to reach a given Hb target. The route of administration of erythropoietin-alfa is determined largely by convenience in the outpatient setting, which favors the subcutaneous route with the

added realization that even in the face of IV access, erythropoietin-alfa is more cost-effective when administered subcutaneously. In children, the psychological impact of frequent and/or painful injections is also an important consideration when determining the dosing route. The 2008 NAPRTCS annual report revealed that 96% of children on PD were administered an ESA by the subcutaneous route as opposed to only 14% of the hemodialysis (HD) population.[18] Preloaded erythropoietin-alfa injections are more painful than those from multidose vials because the former do not contain benzyl alcohol that acts as a local anesthetic.

A longer acting erythropoietin, darbepoetin-alfa, has been shown to be an effective alternative ESA with less frequent (once weekly or every other week) administration required.[142–144] One report provided evidence that the injections of this ESA are more painful than erythropoietin-alfa.[143] The usual staring dose of darbepoetin-alfa for a ESA naïve patient is 0.45 μg/kg/wk, whereas for patients converting from erythropoietin-alfa, the manufacturer's recommended dose is 1 μg darbepoetin-alfa for every 200 Units of erythropoietin-alfa. However, a study on a small number of pediatric patients suggests that the conversion dose of erythropoietin-alfa to darbepoetin is more likely to be closer to 0.5 μg for every 200 Units, although the authors themselves suggest a wide range of doses, 0.25 to 0.75 μg/kg/wk, as being reasonable for the initial conversion between therapies.[142]

The second key component of anemia management in patients with CKD is iron therapy. This is most important as iron deficiency is the most common reason for ESA "resistance," a complication that may in part be related to elevated levels of hepcidin[139] (*vide supra*). It is recommended that the results of iron status tests (serum ferritin and TIBC), Hb level, and ESA dose should be interpreted collectively to guide iron therapy. Similar to the adult population, several studies have shown that the supplementation of iron in children receiving ESA therapy allows for a reduction in the ESA dose required per unit of Hb level achieved.[145] Iron supplementation in children with CKD varies in terms of dose and type of preparation. Many children with CKD stages 2–4 benefit from and receive oral iron therapy. As per the 2008 NAPRTCS annual report, 28% of children with CKD were receiving oral iron therapy.[18] The recommended doses of oral elemental iron ranges from 2–3 mg/kg/day up to 6 mg/kg/day (maximum 300 mg) in 2 to 3 divided doses.[130] Iron should be taken 2 hours before or 1 hour after all calcium-containing phosphate binders and food to maximize GI absorption. Some patients, however, may not tolerate or may fail to respond to oral iron therapy, possibly as a result of elevated hepcidin levels, and will require intravenous iron. In contrast to adults in whom large single doses of IV iron have been administered at infrequent intervals (e.g., monthly), no comparable data are available in children. To date, only ferric gluconate has been approved as an IV source of iron for children receiving HD.[141] As mentioned previously, it is important to remember that it is possible to have acceptable levels of both TSAT and ferritin and still benefit from IV iron if the patient has so-called functional iron deficiency; therefore, occasionally, after careful assessment of the risk and benefits, a "trial" of IV iron in an anemic patient—even one who appears iron replete—may be indicated.[146] Iron status tests should be performed every month during initial ESA treatment and at least every 3 months once a stable ESA treatment regimen has been reached in patients with CKD.[130]

The goal for the rate of increase in Hb level should be an increase of 1–2 g/dl per month.[130] At the initiation of treatment with rHuEPO or when making significant changes to the rHuEPO dosage, the Hb level should be monitored every 1 to 2 weeks; the frequency of monitoring can be decreased to at least once monthly when the patient has reached a target Hb level and is on a stable dose of ESA (Figure 17-2).

In the absence of definitive evidence in pediatrics to support the association of benefit or harm to any given level of Hb for an individual child, the target Hb is 10–12 g/dl for patients receiving ESA and iron therapy, identical to that for adults. Observational data in pediatrics do support such a recommendation.[127] Likewise, based on safety concerns from studies in adults in which cardiovascular complications were noted in association with elevated Hb values, target Hb levels ≥13 g/dl in children are not recommended.[132] It should be noted, however, that there are currently no studies in children that have revealed an increased risk for complications in association with Hb levels ≥13 g/dl. Nevertheless, given the available evidence for an increased risk of cardiovascular death and coronary artery calcification in older children with CKD, it would seem prudent to carefully weigh the individual child's potential benefit of an incremental increase in quality of life, school performance, or exercise tolerance from a Hb level ≥13 g/dl, to the uncertain but potentially devastating risk of myocardial infarction or stroke.[132,147]

The impact of implementing the principles noted previously has been modest at best, as the mean Hb level for children at dialysis initiation has increased from 9.1 g/dl during 1996–2000 to 9.7 g/dl during 2001–2005.[148] This was associated with a corresponding increase in the ESA dose but with variable utilization of the therapy; although overall the proportion of children receiving an ESA prior to dialysis initiation increased from 34.5% to 39.1% during the same time periods, in 2005, only 30.2% of patients 15–19 years received an ESA before starting dialysis as compared to over 45% of patients younger than 14 years. In addition, a higher proportion of white children received an ESA compared to African Americans—41.9% versus 28.8%; likewise, more than half of those with cystic kidney disease received an ESA compared to 37.1% and 25.5%, respectively, of those with primary or secondary glomerulonephritis.[148]

MINERAL AND BONE DISORDERS

Bone disease is a universal complication of CKD, and it encompasses a spectrum of skeletal disorders ranging from the high-turnover lesions of secondary hyperparathyroidism to the low-turnover adynamic bone disease.[149] Over the last decade, evidence has emerged that the abnormalities of bone and mineral metabolism that occur in patients with CKD are also responsible for extraskeletal calcification and increased cardiovascular morbidity, even in children.[150,151] As a result, the term *CKD-Mineral and Bone Disorder (CKD-MBD)* has been coined to describe this broader clinical syndrome that develops as a systemic disorder of mineral and bone

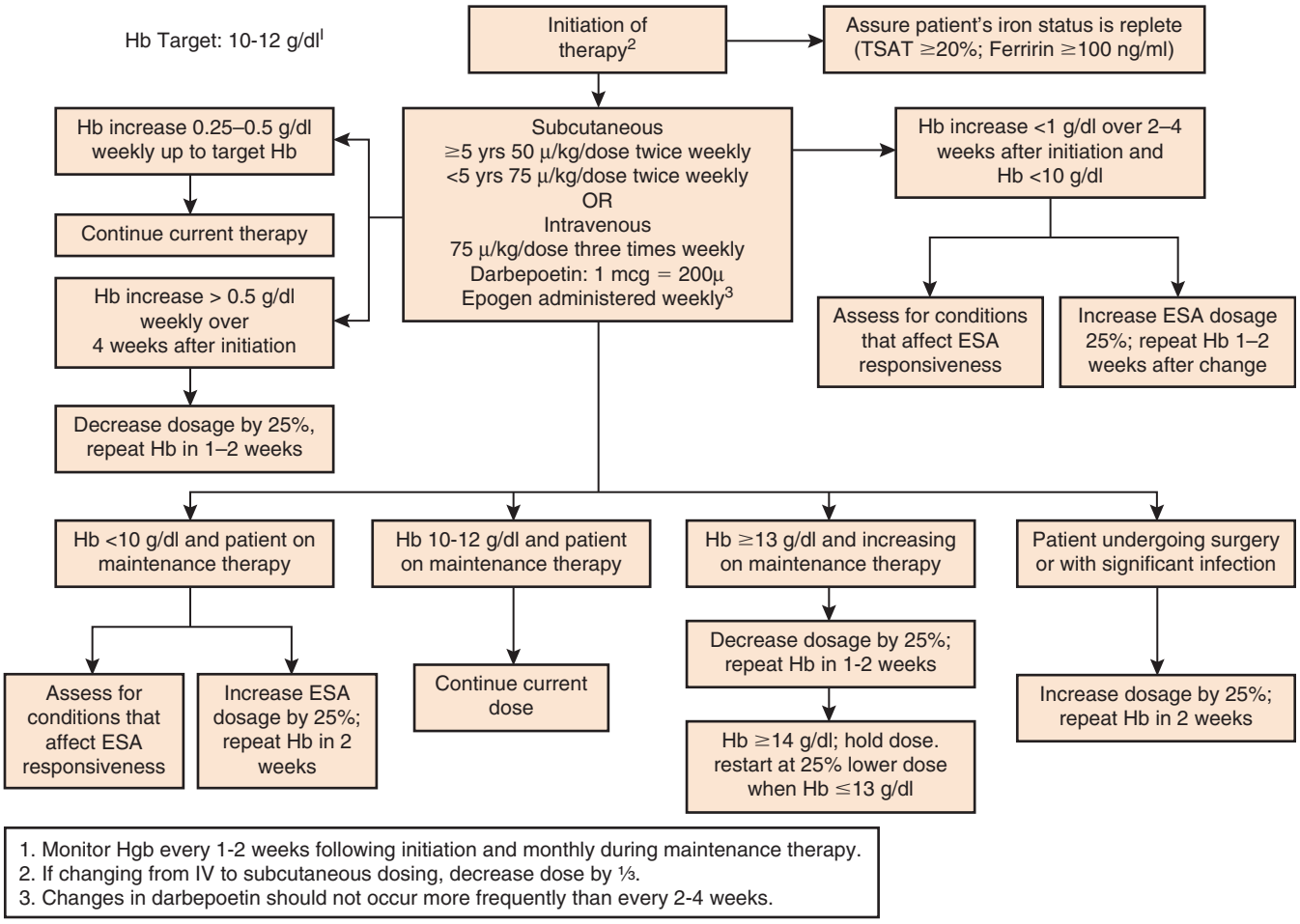


FIGURE 17-2 Management of ESA therapy.

metabolism in patients with CKD.[152] Similar factors are involved in the pathogenesis of bone mineral disorders in adult and pediatric patients with CKD and include disturbances in calcium and phosphorus homeostasis, reduced synthesis of the active form of vitamin D (1,25-dihydroxycholecalciferol), altered regulation of parathyroid hormone (PTH), impaired renal clearance of PTH fragments, and accumulation of the phosphaturia hormone fibroblast growth factor (FGF)-23.[153] FGF-23 is a novel hormone secreted from bone forming osteoblasts whose phosphaturic actions are PTH-independent, and in contrast to PTH, FGF-23 inhibits renal 1α-hydroxylase activity. While it is well-recognized that hyperphosphatemia, hypocalcemia, and a progressive decline in calcitriol levels all stimulate PTH secretion and have long been known to contribute to the pathogenesis of secondary hyperparathyroidism (SHPT),[154] a study involving a large number of adult patients with CKD revealed that SHPT actually developed at a time when the serum calcium and phosphorus levels were still normal.[155] This led some researchers to believe that the deficiency of calcitriol, which occurs during the earlier stages of CKD, may be the primary mechanism initiating SHPT. Recent studies, however, have shown that there is a significant increase in the FGF-23 level early in the course of CKD that may help maintain normal serum phosphate levels but at the cost of suppressing calcitriol levels and worsening SHPT.[153] In addition, recent studies have shown a widespread prevalence of "nutritional" vitamin-D deficiency in the CKD population, which may also play a role in the development of HPT in those patients with early CKD.[156]

Although the pathophysiological mechanisms responsible for the vascular calcification that results from CKD-MBD have not yet been fully elucidated, a direct correlation between the presence/severity of calcification and the levels of serum phosphorus, calcium-phosphorus product, and PTH, the dosages of calcium containing phosphorus binders and calcitriol, and the duration of dialysis has been observed.[150,157,158] It is noteworthy that unlike the calcification that characterizes atherosclerotic plaques and is localized to the intimal layer of the vasculature, vascular calcification in CKD is mainly localized in the medial layer of blood vessels. Current research suggests that the pathogenesis of vascular calcification is much more complicated than simple passive mineralization and is likely an active cell mediated process.[159,160] Vascular smooth muscle cells have been shown to transform to osteoblast like cells and express bone matrix proteins such as osteopontin, osteocalcin, and type I collagen. This transformation is facilitated by the upregulation of core binding factor alpha 1 (Cbfa1), a transcription factor critical for osteoblast differentiation, in the presence of uremic toxins.[161] Nonetheless, there is also a

subset of patients who do not develop vascular calcification despite exposure to a similar uremic environment. This may in part be explained by the findings in a recent study by Shroff and colleagues in which the authors demonstrated that the levels of Fetuin-A, a prototypic calcification inhibitor, were significantly lower and the levels of osteoprotegerin (a soluble decoy receptor for the receptor activator of nuclear factor-κB ligand that stimulates osteoclastic bone resorption) were significantly higher in children with coronary or valvular calcification on CT scan than in those without evidence of calcifications.[162]

With the recognition of early onset coronary artery calcification and increased cardiovascular morbidity in patients with CKD, there has been a significant shift in the recommended management of mineral and bone disorders that is likely to change even further with additional unraveling of the pathogenic mechanisms. Current management of CKD-MBD hinges on the concept of achieving an optimum CKD stage related level for serum PTH, which is in a range that is associated with normal bone turnover without increasing the risk for ectopic calcification. Maintaining normal bone turnover is important for two reasons: first, to prevent bone deformity, pain, and fractures, and to optimize growth; and second, to prevent soft tissue calcification. The risks of extra skeletal calcification are thought to be increased with both low and high bone turnover states, because both scenarios result in high plasma calcium and phosphate levels; low bone turnover because of the inability of bone to buffer changes in plasma calcium and phosphate, and high turnover because high PTH levels mobilize calcium and phosphate from bone, increase tubular reabsorption of calcium, and promote gut absorption of calcium and phosphate by hydroxylation of 25 (OH) vitamin D_3. In the absence of bone biopsy, an invasive procedure but clearly the "gold standard" as a means to evaluate bone turnover, the PTH level is currently used as the best available surrogate marker of bone turnover. The optimum range of PTH in CKD likely changes with the progression of disease due to increasing skeletal resistance to PTH when increasingly higher PTH levels appear to be necessary to maintain normal bone turnover. So far only a small number of studies in children have attempted to identify the range of PTH levels that correlates with normal bone histology, and most of the data have been generated in the ESRD and not the CKD population. The ability of the PTH level to accurately distinguish between low and normal bone turnover is not clear, especially in patients with CKD, and thus the target range for children remains controversial.[163] Nevertheless, recommended targets have been published (Table 17-4), and newer recommendations will be forthcoming from the Kidney Disease: Improving Global Outcomes (KDIGO) initiative.[164] Irrespective of the target value, the PTH level can be manipulated by the control of plasma calcium and phosphate by diet, the use of phosphate binders, and judicious usage of vitamin D and its analogs as detailed in the current K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with CKD[165] and in the recently published K/DOQI Nutritional Guidelines for Children with CKD.[39]

TABLE 17-4 Target Range of Serum PTH by Stage of CKD

CKD STAGE	GFR RANGE (ml/min/1.73 m^2)	TARGET SERUM PTH (pg/ml)
3	30-59	35-70
4	15-29	70-110
5, 5D	<15	200-300

(Adapted from National Kidney Foundation, K/DOQI Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease, Am. J. Kidney Dis. 46 [Suppl. 1] [2005] S1-S122.)

Parathyroid Hormone

The development of the second generation immunometric PTH assay (2nd PTH-IMA) helped clarify the reason for maintaining higher than normal levels of PTH in patients with advanced CKD to prevent the development of adynamic bone disease. The 1st PTH-IMAs detects not only the intact hormone, but also PTH fragments truncated at the amino-terminus, for example, PTH (7–84).[166] In contrast, the 2nd PTH-IMA uses a detection antibody raised against the first four amino-terminal amino acids and recognizes only PTH (1–84) and possibly PTH fragments that are truncated at the carboxyl-terminus, but not the PTH (7–84).[167,168] Thus, first generation PTH-IMAs overestimate the true concentration of PTH (1–84) in serum or plasma, both in patients with ESRD and those with normal kidney function.[167] In patients undergoing dialysis therapy, the PTH concentrations measured with the 1st PTH-IMA are on average 40%–50% higher than those measured with 2nd PTH-IMA.[168,169] Further studies have indicated that one or more PTH (1–84) fragments, such as PTH (7–84), may actually antagonize the calcemic actions of PTH (1–84) and may modulate bone metabolism through a receptor distinct from the type I PTH/PTHrP receptor.[168] Despite the distinct differences, studies comparing the two assays in children have shown them to have similar predictive values in determining the specific bone histology.[169] Therefore, and also because of limited experience and availability of the 2nd generation assays, 1st generation assays are currently recommended.[165]

Calcium

Adequate dietary calcium intake during childhood is necessary for skeletal development and acquisition of optimal peak bone mass.[170] The current recommendation is that patients with CKD should achieve a calcium intake of 100% of the DRI.[171] Infants and young children usually meet the DRI for calcium with the consumption of adequate volumes of breast milk/formula. Unfortunately, the largest sources of dietary calcium for most persons are dairy products that are also rich in phosphorus; in turn, phosphorus restriction universally leads to a decreased calcium intake. In these situations, calcium supplementation may be required because low phosphorus, high-calcium-containing foods such as collards, dandelion greens, kale, rhubarb, and spinach usually do not make up a substantial part of a child's diet. Several products fortified with calcium such as fruit juices and breakfast foods are commercially available, and limited studies have suggested that the bioavailability of calcium from these products is at least comparable to that of milk. Calcium can also be supplemented in medicinal forms such as carbonate, acetate, and gluconate salts of calcium that are commonly used as phosphate binders. When used for calcium supplementation alone, ingesting

these products between meals maximizes calcium absorption. Chloride and citrate salts of calcium should be avoided because the former may lead to acidosis in patients with CKD, and the latter may enhance aluminum absorption.

On the other hand, excessive calcium intake in conjunction with activated vitamin D analogs can lead to 1) hypercalcemia, 2) adynamic bone disease, and 3) systemic calcification. Accordingly, the K/DOQI guidelines recommend that the combined elemental calcium intake from nutritional sources and phosphate binders should not exceed two times the DRI for age, except for ages 9–18 years (both genders) where two times the DRI (2600 mg) exceed the tolerable upper intake level (UL) of 2500 mg.[171] The serum level of total corrected calcium should be maintained within the normal range (8.8–9.5 mg/dl), preferably toward the lower end and definitely not more than 10.2 mg/dl, while the serum calcium and phosphorus product should be kept below 55 mg/dl in adolescents >12 years and <65 mg/dl in younger children.[165]

Phosphorus

In an effort to prevent/control CKD-associated bone disease and CVD, serum phosphorus concentrations above the normal reference range for age (Table 17-5) should be avoided in patients with advanced CKD. However, even during the earlier stages of CKD when the serum phosphorus levels are typically within normal range, the dietary phosphorus load is an important determinant of the severity of hyperparathyroidism. Dietary phosphorus restriction decreases increased PTH levels and increases $1,25(OH)_2D$, whereas dietary phosphorus intakes approximately twice the DRI for age aggravate hyperparathyroidism, despite little or no change in serum phosphorus levels (likely the result of elevated FGF-23 levels).[172] It is important to note that the higher physiological serum concentrations of calcium and phosphorus that are observed in healthy infants and young children presumably reflect the increased requirements for these minerals by the rapidly growing skeleton. Rickets due to phosphorus deficiency can occur in preterm infants whose diet provides insufficient amounts of phosphorus and in infants and children with hypophosphatemia due to inherited disorders of renal phosphate transport. Hence, when dietary phosphorus is restricted to control hyperphosphatemia and SHPT in children with CKD, subnormal serum phosphorus values are equally important to avoid. Recently published recommendations suggest that in children with CKD whose serum PTH concentration exceeds the target range (see Table 17-4) but whose serum phosphorus concentration remains normal, the dietary phosphorus intake should be restricted to 100% of the DRI; in contrast, the intake should be restricted to 80% of the DRI when the serum phosphorus concentration exceeds the normal reference range for age.[39] After initiation of dietary phosphorus restriction, it is suggested that the serum phosphorus concentration be monitored at least every 3 months in children with CKD stages 3 to 4 and monthly with more advanced stages.

Despite the need to restrict dietary phosphorus, most clinicians recognize that an overly strict dietary phosphorus restriction below the levels recommended previously is often not only impractical, but also can be ill advised because it may lead to an inadvertent poor dietary protein intake. In addition, extremely low-phosphorus diets are typically unpalatable. While young infants may be effectively managed by a low-phosphorus-containing milk formula such as Similac PM 60/40® (Ross Laboratories, OH) or Good Start® (Carnation National Products), most other patients with CKD require oral intestinal phosphate binders to control hyperphosphatemia. Phosphorus control is particularly difficult in vegetarians because for the same total quantity of dietary protein delivered, the phosphorus content is greater in protein derived from vegetable sources (average 20 mg of phosphorus per gram of protein) versus animal protein (average 11 mg of phosphorus per gram of protein). However, the bioavailability of phosphorus from plant-derived food is very low; therefore, despite their higher specific phosphorus content, some plant sources of protein may actually result in a lower rate of phosphorus uptake per mass of protein than meat-based foods.[39] Whereas food labels rarely state the phosphorus content, chocolates, nuts, dried beans, and cola soft drinks are rich in phosphorus and should be avoided; nondairy creamers and certain frozen nondairy desserts may be used in place of milk and ice cream.

Aluminum hydroxide and aluminum carbonate were widely used as phosphate binders in the past, but their use was abandoned (other than on rare occasions, for very restricted periods of time, and with a closely monitored low-dose [<30 mg/kg per day] until more definitive therapy is instituted and effective) once they were found to be associated with severe toxicity in adults and children with renal insufficiency. Currently, calcium-containing salts[173] such as calcium carbonate and calcium acetate are commonly used as phosphate binders, with the latter often reported to be the more effective of the two.[174] To be maximally effective, their intake should coincide with that of meals or snacks. The optimal timing for the administration of binders with tube feedings has not been clearly defined. As noted previously, calcium-containing phosphate binders also serve as an important source of supplemental calcium. However, with recognition of the association between calcium-containing phosphate binders and the development of coronary-artery calcification in young adults who started dialysis as young children[150,157] (*vide supra*), recent attention and practice have been focused on the use of calcium and aluminum-free phosphate binders such as Sevelamer hydrochloride (RenaGel®).[175] Although not yet approved for use in children, sevelamer hydrochloride has been shown to be

TABLE 17-5 Age-Specific Normal Ranges of Blood Ionized Calcium, Total Calcium, and Phosphorus

AGE	IONIZED CALCIUM (mmol/L)	TOTAL CALCIUM (mg/dl)	PHOSPHORUS (mg/dl)
0-5 mo	1.22-1.4	8.7-11.3	5.2-8.4
6-12 mo	1.2-1.4	8.7-11	5.0-7.8
1-5 y	1.22-1.32	9.4-10.8	4.5-6.5
6-12 y	1.15-1.32	9.4-10.3	3.6-5.8
13-20 y	1.12-1.3	8.8-10.2	2.3-4.5

(Adapted from National Kidney Foundation, K/DOQI Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease, Am. J. Kidney Dis. 46 [Suppl. 1] [2005] S1-S122.)

effective in lowering serum phosphorus levels in children receiving maintenance dialysis[175] and with a lower risk of hypercalcemia in comparison to calcium-containing binders.[176] Furthermore, its use has been associated with slowing of the progression of vascular calcification in adults when compared to calcium-containing binders. The survival benefit[177] noted in patients receiving this medication may also be related to its beneficial effects on the lipid profile. Although the hydrochloride salt of sevelamer has been known to cause acidosis, this is likely to be prevented with the use of the new modified agent, sevelamer carbonate (Renvela®). Pretreatment of breast milk, infant formula, and cow's milk with sevelamer has been shown to effectively reduce the phosphorus content in the supernatant by 80%–90%.

Lanthanum carbonate (Fosrenol®), a newer calcium- and aluminum-free binder with high affinity for phosphorus and minimal intestinal absorption, has recently become available. Lanthanum has been shown to accumulate in tissues without any correlation with its plasma level.[178] In large part because of its deposition in bone in adults and its unknown long-term effects on the growing skeleton, its use is not recommended for pediatric patients with CKD.

TABLE 17-6 Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Children with CKD

SERUM 25(OH)D (ng/ml)	DEFINITION	ERGOCALCIFEROL (VITAMIN D_2) OR CHOLECALCIFEROL (VITAMIN D_3) DOSING	DURATION (mo)
<5	Severe vitamin D deficiency	8000 International Units/d orally or enterally × 4 wk or (50,000 International Units/wk × 4 wk); then 4,000 International Units/d or (50,000 International Units twice per mo for 2 mo) × 2 mo	3
5-15	Mild vitamin D deficiency	4000 International Units/d orally or enterally × 12 wk or (50,000 International Units every other wk, for 12 wk)	3
16-30	Vitamin D insufficiency	2000 International Units daily or (50,000 International Units every 4 wk)	3

(Adapted from National Kidney Foundation, K/DOQI Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease, Am. J. Kidney Dis. 46 [Suppl. 1] [2005] S1-S122.)

Vitamin D

Recent clinical evidence suggests a high prevalence (typically 80% to 90%) of nutritional vitamin D insufficiency in both children and adults with CKD.[156] In a recent publication, Ali and colleagues reported 20%–75% prevalence of vitamin D deficiency (25(OH)D <15 ng/ml) in children with CKD stages 1–5, with higher prevalence rates in Hispanics and African Americans, likely due to increased melanin content in their skin.[156] This insufficiency may aggravate SHPT in patients with CKD as the availability of $25(OH)_2$ D becomes a rate limiting step for the synthesis of $1,25(OH)_2$ D. Accordingly, the latest K/DOQI Pediatric Nutrition Guidelines suggest checking the serum $25(OH)_2$ D levels once per year in children with CKD stages 2–5.[39] If the serum level of $25(OH)_2$ D is <30 ng/ml, supplementation with vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) is suggested, with the specific dosing regimen dependent on the severity of the deficiency (Table 17-6). During the repletion phase, serum levels of calcium and phosphorus should be measured 1 month following the initiation or a change in the dose of vitamin D and at least every 3 months thereafter. Once patients are replete with vitamin D, supplemental vitamin D should be continued and $25(OH)_2$ D levels checked yearly.[39,165]

In patients with CKD whose serum levels of 25(OH) D are >30 ng/ml and PTH levels exceed the target range for the CKD stage, therapy with an active vitamin D sterol (calcitriol) or dihydrotachysterol (requires only hepatic hydroxylation for activation) should be initiated, as long as the serum level of corrected total calcium is <10 mg/dl and the serum level of phosphorus is less than the age-appropriate upper limit.[165] Calcitriol may be given orally or intravenously with initial doses ranging from 5–10 ng/kg/day. It may be administered daily or intermittently with equivalent efficacy in controlling SHPT.[179] Calcitriol usage does increase intestinal phosphorus absorption by 50% and thus may worsen hyperphosphatemia and necessitate modification of dietary and/or binder therapy. These preparations are often started early in the course of CKD on the basis of an elevation of the intact serum PTH and serum alkaline phosphatase level. As suggested previously, one of the serious complications associated with the use of the activated vitamin D metabolites is the development of hypercalcemia, and excessive doses of these agents have been associated with the development of vascular calcifications. In turn, several newer noncalcemic vitamin D analogues such as paricalcitol (19-nor-1, 25-dihydroxyvitamin D_2)[180] and doxercalciferol (1α-hydroxyvitamin D_2)[181] have been developed to selectively suppress the parathyroid gland with a lower incidence of hypercalcemia when compared to current agents. These agents have been used successfully in children.

Finally, calcimimetic agents such as cinacalcet increase the sensitivity of the calcium sensing receptor in the parathyroid gland to ionized calcium and can also be used to treat hyperparathyroidism. Cinacalcet has been shown to effectively lower serum PTH levels in adult ESRD and CKD patients.[182] Although Cinacalcet has not been approved for use in children, a recent open-label study of its dosing in pediatric ESRD patients showed that it was effective and well-tolerated without any significant adverse effects.[183]

CARDIOVASCULAR DISEASE

Systemic atherosclerosis and CVD are usually viewed as unique problems of adulthood, and adult patients with CKD do suffer significantly increased rates of morbidity and mortality secondary to CVD as compared to the general population.[184–186] Nonetheless, it has become increasingly evident that the systemic process of atherogenesis begins during childhood as many pediatric patients with CKD presumably undergo years of accelerated atherosclerosis as they mature toward later life.[187] In fact, CVD is the leading cause

of morbidity and mortality in children with CKD, accounting for approximately 25% of total deaths.[105,188,189] These rates are almost 1000 times higher than in comparably aged individuals without renal disease, resulting in a life expectancy that is shortened by as much as 40 to 60 years.[189,190] However, it is important to note that the common cardiovascular causes of mortality in adults, such as coronary artery disease and congestive heart failure, are rare in children with CKD who on the other hand experience arrhythmias, valvular disease, and cardiomyopathy.[191]

The risk factors for cardiac and vascular injury in children with CKD are by and large similar to those for adults. In addition to the multitude of uremia-related risk factors for atherosclerotic CVD such as anemia, malnutrition, chronic inflammation and hyperparathyroidism, the traditional risk factors for CVD such as hypertension and hyperlipidemia are also widely prevalent in children with CKD. Indeed, hypertension develops during the early stages of CKD in almost half (48%) of the children.[192] Analysis of the data from the CKiD study revealed that 54% of 432 children with CKD stages 2–5 had either systolic or diastolic BP $\geq$95th percentile or a history of hypertension plus current antihypertensive use. Hypertension was more common in African American children, even after adjustment for age, cause, and duration of CKD, CKD stage, degree of proteinuria, obesity, and antihypertensive use.[193] Hyperlipidemia in children with CKD is also very common because 25%–53% develop an abnormal lipid pattern before reaching ESRD.[104] This combination of traditional and uremia-related risk factors initiates and accelerates CVD in the pediatric population with CKD. The pathophysiology of CVD in CKD is characterized by two potentially concurrent processes of cardiac remodeling and vascular injury.

Cardiac remodeling involves both concentric and eccentric left ventricular hypertrophy (LVH); while the former is secondary to increased resistance from hypertension, the latter occurs due to volume overload and anemia. LVH is defined as a left ventricular mass (LVM) index greater than the 95th percentile for age. LVM is measured by standard echocardiography, and the LVM index is calculated as left ventricular mass in grams divided by height in meters raised to a power of 2.7 ($g/m^{2.7}$). In children with CKD, LVH develops early during mild-to-moderate CKD and progresses with worsening kidney function. About one-third of children with mild-to-moderate CKD have an increased LVM index, and it progresses as kidney function deteriorates.[194,195] In a 2-year prospective longitudinal study of 31 pediatric subjects with CKD stages 2–4, Mitsnefes and colleagues[196] showed that a substantial proportion (19%) of children had a significant increase in the LVM index, and 32% of the patients who initially had a normal LVM index developed LVH over the study period. The same authors and others have also demonstrated that at initiation of maintenance dialysis, 69%–82% of pediatric patients have evidence of LVH. While the correlation between BP and LVH has repeatedly been demonstrated in children with ESRD,[122] the presence of a similar relationship during the earlier stages of pediatric CKD is uncertain. In fact, a detailed cross-sectional analysis of children with CKD from the Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial did not demonstrate any relationship between office BP or ambulatory blood pressure monitoring (ABPM) parameters and LVH.[195] In contrast, the analysis of longitudinal data revealed that an increase in the nighttime systolic BP load was independently associated with an increase in LVM index over time, suggesting that a persistent and chronic elevation of BP might be most important in the development of LVH.[196] Other factors associated with cardiac hypertrophy in children are likely similar to those in adults with CKD. As in adults, most studies of children with CKD have found a significant relationship between low hemoglobin levels and an increased LVM index.[195,196] Likewise, elevated PTH levels have been shown to be associated with the progression of LVH in children with stages 2–4 CKD.[196] Possible mechanisms of parathyroid-induced cardiac hypertrophy in CKD include a direct effect of PTH on cardiomyocytes and an indirect effect through elevated BP.[197]

Long-standing cardiac hypertrophy ultimately leads to decreased subendocardial perfusion and myocardial fibrosis, all of which results in maladaptive LVH with systolic and/or diastolic dysfunction and an increased risk of arrhythmia generation. In contrast to adults in whom systolic dysfunction is frequently associated with early cardiac failure and decreased survival, in children with CKD, systolic LV function is usually preserved while diastolic dysfunction is often the initial abnormality.[198] The clinical significance of diastolic dysfunction in pediatric patients with CKD is currently unknown.

The second process, vascular injury, includes atherosclerotic and/or arteriosclerotic changes that are eventually complicated by calcification.[199,200] Atherosclerotic changes begin with penetration of the vascular intima with lipid-containing foam cells (macrophages), followed by the subsequent accumulation of smooth muscle cells and collagen fibers to form a plaque or atheroma. These lesions characteristically have a patchy distribution along the length of the artery and cause local stenosis and occlusion. Arteriosclerosis, on the other hand, is characterized by arterial stiffening involving the entire arterial tree, but in particular the elastic arteries. Furthermore, unlike atherosclerosis, arteriosclerosis causes both intimal and medial thickening and results in increased vascular wall thickness and lumen enlargement. This arterial stiffening leads to an increased systolic BP and pulse pressure. It is noteworthy that in CKD, arteriosclerosis can occur in the absence of significant atherosclerotic disease.[201] The pathophysiological mechanisms responsible for the vascular calcification are complex (*vide supra*); however, there is a direct correlation between the presence/severity of calcification and the levels of serum phosphorus, calcium-phosphorus product, and PTH, the dosages of calcium containing phosphorus binders and calcitriol, and the duration of dialysis.[150,157,158]

As mentioned before, vascular abnormalities in children develop in parallel with cardiac abnormalities early in the course of CKD and become more severe as ESRD is reached.[151,202] Early vascular abnormalities can be assessed by measuring carotid intima media thickness (IMT) and endothelial dysfunction. The latter is measured by flow-mediated dilation (FMD) of the brachial artery as the vasodilatory response to nitric oxide is diminished in the presence of endothelial injury.[203] Interestingly, the severity of vascular changes in children with CKD stages 2–5 is

influenced by conventional CVD risk factors such as hypertension and dyslipidemia, while in children receiving dialysis, hyperphosphatemia, hyperparathyroidism, and treatment with calcium-containing phosphate binders are major determinants of arterial abnormalities.

Recommendations for the evaluation and treatment of CVD risk factors in children with CKD have primarily been derived from adult data and clinical experience and focus upon traditional risk factors such as hypertension and dyslipidemia with a goal to prevent the development and delay the progression of cardiomyopathy and atherosclerosis. According to current recommendations, the target blood pressure in children should be lower than the 90th percentile for age, gender, and height or <120/80 mmHg, whichever is lower.[204,205] While ABPM is currently not a part of the standard recommendations for evaluation of hypertension in children with CKD, several studies in non-CKD adults and in children have shown the superiority of ABPM over clinic BP (CBP) monitoring in predicting cardiovascular morbidity and mortality.[206–208] Recently, Dionne and colleagues found that ABPM detected BP abnormalities in nearly 50% of pediatric CKD patients that were otherwise not detected by CBP.[209] Similarly, Mitsnefes and colleagues detected nighttime systolic and diastolic hypertension in 12 (41%) children with CKD, and reported a significant correlation between 24-hr systolic BP load and LVM index.[210] ABPM may therefore serve as a better means of predicting end organ injury than CBP in children with CKD.

ACE inhibitors and ARBs, both of which interrupt the renin-angiotensin system (RAS), are advocated as the optimal agents for the management of hypertension in CKD.[204] RAS antagonists seem to offer better preservation of kidney function than other antihypertensive agents,[211] especially in patients with proteinuria.[212] The potential mechanisms of renoprotection are discussed later in the chapter (*vide infra).* The evidence of renoprotection by RAS antagonists and their antihypertensive efficacy with few side effects has, in turn, led to the widespread use of these agents in pediatric patients with CKD despite few published pediatric data. Recent cross-sectional analysis of CKiD study data showed that there was significant association between the absence of ACE inhibitor or ARB usage and uncontrolled hypertension.[193] Calcium-channel blockers (CCBs) are also safe and effective antihypertensive agents in patients with CKD. However, CCBs of the dihydropyridine type (amlodipine, nifedipine) have been shown to increase proteinuria,[213] and in some large scale trials in adults have been associated with poorer outcomes in comparison to RAS antagonists. In contrast, nondihydropyridine CCBs such as verapamil and diltiazem have been shown to have effects equivalent to ACE inhibitors in slowing the progression of CKD in adult diabetic patients.[214] The latter agents are known to cause prolongation of the PR interval,[215] and there are no published safety data regarding their use in children with hypertension. Diuretic therapy should also be considered in children with CKD to address the sodium and fluid overload that may be present in patients who do not have salt-losing nephropathies. Thiazide diuretics may be used in patients with earlier stages of CKD, but they are not effective when the GFR falls below 30 ml/min/1.73 m^2 when loop diuretics should instead be used. Beta blockers, α-adrenergic agents (prazosin, clonidine), and other vasodilators (hydralazine, minoxidil) may also be considered for therapy, with their selection and continued usage dependent on their efficacy and side effect profile in the individual patient.

As mentioned before, the pattern of dyslipidemia seen in CKD has been characterized as "atherogenic" and is an independent contributor to the development of CVD (*vide supra*). The assessment of dyslipidemia should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides. The optimal management of dyslipidemia in children with CKD is not clearly defined and is discussed in the section on Nutritional Issues (*vide supra*). Nonetheless, all children with dyslipidemia should follow the recommendations for therapeutic lifestyle changes, which include diet modification with a reduction in saturated fat intake, increase in fiber intake, and moderate physical activity. As mentioned before, a judicious use of lipid lowering drugs (statins) may be considered in children older than 10 years with LDL cholesterol ≥160 mg/dl or a combination of fasting triglyceride ≥200 and non-HDL cholesterol ≥160 mg/dl.[104] There is no information on the efficacy of lipid-lowering therapies on cardiovascular morbidity or mortality in pediatric CKD patients. Therefore, the presumed benefit in children is extrapolated from adult studies. However, statin therapy has been proven to be effective in improving endothelial function in children with hypercholesterolemia.[216]

In summary, early evaluation and an aggressive management approach to include effective blood pressure control, anemia management, control of dyslipidemia, and prudent use of phosphate binders and vitamin D therapy for management of secondary HPT is essential to decrease CVD-related morbidity and mortality. The role of folic acid and anti-inflammatory therapy to treat elevated homocysteine levels and inflammation, respectively, in children with CKD awaits further study.

PROGRESSION OF CHRONIC KIDNEY DISEASE

The major health consequences of CKD are, for the most part, associated with its relentless progression to ESRD; however, the natural history of its early stages is variable and often unpredictable. Most available data demonstrate a slower progression of CKD in children with congenital renal disorders compared to those with glomerular diseases. In addition, the progression of established CKD is influenced by a variety of risk factors, some of which (e.g., obesity, hypertension, and proteinuria) may be modifiable,[217] whereas others, including genetics, race, age, and gender are not. There is clear evidence from clinical studies that hypertension and proteinuria are the most important independent risk factors for CKD progression, and not surprisingly, normalization of blood pressure and minimization of proteinuria appear to be the two most important measures to preserve residual kidney function (*vide infra*).[218,219]

The impact of proteinuria on the progression of CKD is likely related to the fact that as protein leaks through the diseased glomerulus, it injures the tubular cells and thereby causes interstitial inflammation and subsequent fibrosis and apoptosis in proximal tubular cells.[220,221] The presence of microalbuminuria in adult patients with diabetes is

associated with a 10-fold higher risk of progression to overt nephropathy. Severe proteinuria is also associated with a faster progression of renal deterioration in adult patients with nondiabetic glomerular diseases.[222] Results from the MDRD study supports the concept that proteinuria is an independent risk factor for progression of CKD in adults.[223] Similarly, in the Ramipril Efficacy In Nephropathy (REIN) trial in adults, the degree of proteinuria was the only baseline variable that correlated with a decline of kidney function toward ESRD.[212]

In children with CKD stages 3–4, the European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood demonstrated that proteinuria and hypertension were major independent determinants of CKD progression.[92] Analysis of data from the Italian Pediatric Registry of CRF (ItalKid Project) revealed that proteinuria was an independent predictor of CKD progression, even in children whose renal impairment was due to congenital hypodysplasia.[224] Finally, there is evidence from the ESCAPE trial that residual urinary protein excretion during ACE inhibition is quantitatively associated with CKD progression.[225]

Although proteinuria is an established biomarker of CKD progression, diseases involving a high filtered load of albumin such as minimal change nephrotic syndrome are not typically associated with the presence of renal insufficiency, providing evidence for the limitations of albuminuria in its role as a biomarker. On the other hand, evidence of tubular injury and dysfunction may be manifested by abnormal amounts of small urinary tubular proteins. Studies suggest that the urinary excretion of α 1- and β 2-microglobulin are better predictors of the clinical course of CKD progression. In addition, retinol binding protein (RBP) and N-acetyl-glucosaminidase (NAG) have been shown to be markers of proximal tubular damage and dysfunction, with the former being much more sensitive than the latter for the early detection of tubular impairment. In children with vesicoureteral reflux, evidence of tubular dysfunction as measured by urinary RBP and NAG is frequently noted in patients who have renal scarring, providing evidence of damage that usually precedes the development of albuminuria. Biomarkers of acute kidney injury such as Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Kidney Injury Molecule 1 (KIM-1) are currently being evaluated for their usefulness in the setting of CKD. Finally, new methodologies such as Multidimensional Proteomics Identification Technology (MudPIT) and Selected Reaction Monitoring (SRM)-mass spectrometry are exciting scientific developments that have the potential for identifying clinically useful biomarkers that predict the progression of kidney disease early in its course, at a time when therapeutic interventions may prove particularly beneficial.[226] Research on these investigative techniques is an important component of the multicenter CKiD study.[13]

As mentioned previously, there is clear and consistent evidence that hypertension is a significant and modifiable mediator of CKD progression,[223] based in large part on the results of studies in adults. A significant association between hypertension and progression of CKD in adults has been shown in a review of 26 studies by K/DOQI.[2] Numerous reports have shown that antihypertensive therapy slows the rate of ESRD development, with a linear relationship existing between the median blood pressure achieved on therapy and the rate of CKD progression; the beneficial effect appears to persist well into the normal range of blood pressure.[223,227] Firm evidence for a favorable effect of intensified blood pressure control in adult patients with CKD has resulted in generally lower target blood pressure recommendations in this patient group. Accordingly, in the most recent guidelines proposed by the Joint National Committee in the US (JNC7)[228] and the Guidelines of the European Hypertension Society,[229] 120/80 mmHg has been defined as the upper limit of the "optimal" blood pressure range for adults, particularly in the presence of proteinuria.

In children with CKD, the European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood demonstrated that a systolic blood pressure greater than 120 mmHg was associated with a significantly faster decline in GFR.[92] Similarly, a review of the NAPRTCS database by Mitsnefes and colleagues revealed that hypertensive children with CKD had a more rapid decrease in their estimated GFR or progression to renal replacement therapy than normotensive children with CKD.[192] They also found that systolic hypertension was a significant, independent predictor of disease progression along with patient age, an acquired etiology of CKD, and African American ethnicity.[192] However, it is as yet unknown whether glomerular damage in children correlates with absolute or age-specific relative blood pressure. Therefore, the current recommendation for children with CKD is a targeted systolic and diastolic blood pressure $<$ 90th percentile for age, height, and gender or less than 120/80 mmHg, whichever is lower.[204] This mirrors the recommendations of the National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents.[205] The ESCAPE study group has recently completed its trial that is addressing the question of whether intensified blood pressure control (targeting to below the 50th percentile of 24-h mean arterial pressure) will confer added renoprotection in children with CKD.[230] Publication of the results is eagerly awaited.

A variety of other factors may also contribute to the progression of CKD.[218,231] Obesity is associated with hypertension, albuminuria, and dyslipidemia, all of which can potentially influence the progression of CKD. The incidence of certain glomerulonephritides such as focal segmental glomerulosclerosis, is higher in obese than in lean individuals.[232] The mechanisms by which obesity/metabolic syndrome may initiate and exacerbate CKD remain elusive and largely speculative. Some of the potential mechanisms involve the presence of a proinflammatory state, lipotoxicity, and hemodynamic effects such as glomerular hyperfiltration.[233] Race and genetics appear to be the two nonmodifiable risk factors for CKD progression. The clustering of CKD in families is strongly suggestive of a genetic or familial predisposition in some cases.[234] Studies have suggested the presence of links between CKD and various alterations or polymorphisms of candidate genes encoding putative mediators, including the RAS, and an increased susceptibility to disease progression in disorders such as IgA nephropathy.[235] Additionally, racial factors may play a role in the susceptibility to CKD, as there is a strong concordance of kidney disease in the families of African Americans who have developed ESRD secondary to hypertension.[234] Not only may there be an increased susceptibility to disease, but also there is evidence that the rate of progression of CKD is faster among African American males.[236] Finally,

in a recent analysis of 419 children with CKD stages 2–4, Wong and colleagues observed that Caucasians had significantly lower levels of proteinuria than other ethnicities at any given GFR, irrespective of the underlying kidney disease.[219]

More recently, it has become evident that low birth weight is yet another factor that in some ethnic communities might be associated with a reduction in the number of nephrons and a subsequent predisposition to hypertension and kidney disease in later life.[237] Additionally, regardless of the initial degree of impaired kidney function, puberty seems to be a critical stage for patients with CKD as a steep decline in kidney function often occurs during puberty and in the early postpubertal period.[19] While the specific reasons are yet to be determined, it is speculated that this pattern of progression may be attributable to an adolescent-specific pathophysiological mechanism, possibly related to sex hormones and/or an imbalance between residual nephron mass and the rapidly growing body size. Data collected by NAPRTCS have also revealed that patients whose baseline serum albumin was below 4 g/dl, inorganic phosphorus above 5.5 mg/dl, calcium below 9.5 mg/dl, BUN above 20 mg/dl, or hematocrit below 33% had a significantly higher risk of reaching ESRD ($p < 0.001$).[18] Irrespective of the underlying kidney disease or presence of additional risk factors, it appears clear that the risk of progression to ESRD in childhood is inversely proportional to the baseline creatinine clearance.[18,19] Data pertaining to a variety of risk factors potentially associated with the progression of CKD, including those noted previously, are currently being collected by the CKiD study.[13]

PREVENTION OF CHRONIC KIDNEY DISEASE PROGRESSION

Several antihypertensive and antiproteinuric therapies have shown promising results in slowing the progression of CKD. There is evidence that controlling blood pressure alone decreases proteinuria to some degree, as demonstrated by three large trials: the MDRD study,[223] the Appropriate Blood Pressure Control in Diabetes (ABCD) study,[238] and the African American Study of Kidney Disease and Hypertension (AASK).[239] Whereas the different classes of antihypertensive agents are comparable with respect to their blood–pressure-lowering efficacy, they differ markedly with respect to their effects on proteinuria and CKD progression.[211,239,240] The goal of any antiproteinuric treatment is to reduce proteinuria as much as possible, ideally to <300 mg/m^2/day, a value that appears to be associated with the maximal renoprotective effect.[240,241]

Blockade of the RAS by ACE inhibitors and/or angiotensin II type I receptor blockers (ARBs) has been shown to have the most effective antihypertensive and antiproteinuric effects of all of the agents currently available.[204] RAS antagonists suppress the local angiotensin II tone (ACE inhibitor) or action (ARB), which results in a reduction of intraglomerular pressure and proteinuria, diminished local release of cytokines and chemokines, and alleviated activation of inflammatory pathways. The impact of these actions has attenuated glomerular hypertrophy and sclerosis, tubulointerstitial inflammation, fibrosis, and a normalized central nervous sympathetic tone, the result of reduced renal afferent nerve stimulation. In addition, oxidative stress is reduced independently of the blood–pressure-lowering effect.[242] In adults with diabetic or nondiabetic kidney disease, several randomized trials demonstrate a more effective reduction of proteinuria, usually by 30%–40%, by ACE inhibitors compared with placebo and/or other antihypertensive agents.[240] This is associated with a significantly reduced rate of CKD progression.[212,240,243–245] Very similar results have been seen in randomized studies comparing ARBs to placebo or conventional antihypertensive agents in diabetic nephropathy. It has been reasoned that ACE inhibitors specifically might have a particular renoprotective advantage by inducing the accumulation of vasodilatory and antifibrotic bradykinins; however, the rate of CKD progression was similar in two clinical trials comparing ACE inhibitors and ARB therapy.[246] Furthermore, the size of the advantage of RAS antagonists over other antihypertensive agents remains controversial.[247] The superiority of RAS antagonists in adults does appear to be related to the prevailing degree of proteinuria because ACE inhibitors are believed to provide better renoprotection than other antihypertensive agents in patients with proteinuria exceeding 500 mg/day.[240,241]

Information regarding the efficacy of RAS antagonists for renoprotection in children with CKD is limited. Small uncontrolled studies have provided evidence of stable kidney function in children with sequelae of hemolytic uremic syndrome during long-term ACE inhibitor treatment[248] and in children with CKD and proteinuria who were treated with losartan for 2½ years.[249] An attenuated histopathological progression in children with IgA nephropathy has also been noted in children receiving combined RAS blockade.[250] In contrast, data from the ItalKid study did not show a significant modification of CKD progression by ACE inhibitor treatment in children with hypodysplastic kidney disease compared to matched, untreated subjects.[251] Similarly, in the previously referred to publication from the CKiD study, Wong and colleagues observed the antiproteinuric effect of RAS blockade restricted to those with glomerular diseases as a cause of their CKD.[219] While the ESCAPE trial demonstrated efficient blood pressure control and proteinuria reduction by ramipril in almost 400 children with CKD,[230] an interim analysis of the 3-year results revealed a gradual rebound of proteinuria after the second treatment year. This effect was dissociated from the persistently good blood pressure control and may limit the long-term renoprotective efficacy of ACE inhibitor monotherapy in pediatric chronic kidney disorders.[225]

CCBs are safe and effective as antihypertensive agents in patients with CKD. However, CCBs of the dihydropyridine type (amlodipine, nifedipine) fail to slow the progression of CKD and may even increase proteinuria and promote more rapid CKD progression.[213] In contrast, nondihydropyridine CCB (diltiazem, verapamil) may have some antiproteinuric effect and may therefore be renoprotective.[214] Among beta blockers, metoprolol was shown to have antiproteinuric effects comparable to ramipril in the AASK trial,[239] and the newer beta blocker carvedilol has even better antiproteinuric effects.[252]

Among other means used for renoprotection, experimental evidence suggests that statins may retard CKD progression not only by their lipid-lowering effect, but also by lipid-independent pleiotropic effects through the inhibition

of signaling molecules at several points in inflammatory pathways.[253] To date, no studies have evaluated the usefulness of statins for this indication in children with progressive nephropathies.

Last, limited data do not support a relationship between the use of a low-protein diet and protection from CKD progression. One of the largest trials in adults, the MDRD trial, could not prove any efficacy of a low-protein diet on CKD progression in patients with nondiabetic kidney disease.[254] In children, reducing dietary protein intake to approximately 100% to 125% of the RDA was also ineffective in slowing progressive disease.[92,255] Furthermore, a low-protein diet characterized by quantities of dietary protein below the DRI bears the risk of an adverse effect on growth. Therefore, at present, there is no justification for prescribing low-protein diets to children early in the course of CKD.

A full list of references are available at www.expertconsult.com.

Chapter 18

THE PATHOPHYSIOLOGY OF UREMIA

Matthew K. Abramowitz, M.D., M.S., Timothy W. Meyer, M.D., and Thomas H. Hostetter, M.D.

The word "*uremic*" is generally used to describe those ill effects of renal failure that we cannot yet explain. Hypertension as a result of volume overload, tetany as a result of hypocalcemia, and anemia as a result of erythropoietin deficiency were once considered uremic signs but were removed from this category as their causes were discovered. In the present state of knowledge, uremia may thus be defined as the illness that would remain if the extracellular volume and inorganic ion concentrations were kept normal and the known renal synthetic products were replaced in patients without kidneys (Table 18-1).

Some features of uremia, thus defined, could reflect the lack of unidentified renal synthetic products. But we presume that uremic illness is largely the result of the accumulation of organic waste products that are normally cleared by the kidneys. In general, the study of renal organic waste removal has lagged far behind the study of inorganic ion excretion. A major problem is the multiplicity of waste solutes. The most comprehensive review to date, prepared by the European Uremic Toxin Work Group (EUTox),[1] lists more than one hundred uremic solutes and provides references to chromatographic studies describing others. With so many substances to study, it is hard to establish which ones are toxic. Bergstom[2] suggested criteria for identifying uremic toxins that are analogous to Koch postulates for identifying infectious agents. According to these criteria, a uremic toxin must have a known chemical structure, including the following:

- Its plasma and/or tissue concentrations should be higher in uremic patients than in normal people.
- The high concentrations should be related to specific uremic symptoms that are ameliorated when the concentration is reduced.
- The effects observed in uremic patients should be replicated by raising the solute concentration to uremic levels in normal people, experimental animals, or in vitro systems.

No uremic solute has so far been shown to satisfy these criteria. The likelihood that studies of individual solutes will yield negative results has discouraged research. Most uremic solutes are probably not toxic, and those that are toxic may exert their ill effects when administered in combination only.

The difficulty imposed by the multiplicity of solutes is compounded by the multiplicity of ill effects encountered in uremia. Investigators of uremic toxicity thus face the daunting task of matching a solute or group of solutes to an appropriate endpoint. Many of the effects of uremia are hard to quantify, which makes the problem all the more difficult. This is particularly true of major uremic symptoms such as fatigue, anorexia, and diminished mental acuity.

A further major problem encountered in clinical studies of uremia is distinguishing the effects of uremia from those of related conditions. Paradoxically, the development of dialysis has made uremia harder to study. The severity of the classic uremic symptoms is much attenuated, and patients now suffer from a new illness, which Depner[3] has aptly named the "*residual syndrome*," comprising partially treated uremia and the side effects of dialysis. In most patients, features of the residual syndrome are further combined with the effects of age and of systemic diseases responsible for the loss of kidney function. Disturbance of inorganic ion metabolism,

TABLE 18-1 Symptoms and Signs of Uremia
NEURAL AND MUSCULAR
Fatigue
Loss of concentration ranging to coma and seizures
Sleep disturbances
Anorexia and nausea
Diminution in taste and smell
Cramps
Restless legs
Peripheral neuropathy
Reduced muscle membrane potential
ENDOCRINE AND METABOLIC
Amenorrhea and sexual dysfunction
Reduced body temperature
Reduced resting energy expenditure
Insulin resistance
OTHER
Serositis (including pericarditis)
Itching
Hiccups
Granulocyte and lymphocyte dysfunction
Platelet dysfunction
Shortened erythrocyte life span
Albumin oxidation

TABLE 18-2 Uremic Abnormalities Transferable with Uremic Serum or Plasma
Inhibition of sodium-potassium ATPase
Inhibition of platelet function
Leukocyte dysfunction
Loss of erythrocyte membrane lipid asymmetry
Insulin resistance

including acidemia and hyperphosphatemia, though excluded from our definition of uremia, also undoubtedly contributes to illness in dialysis patients. Given these difficulties, it is not surprising that knowledge of the accumulation of uremic solutes, as later summarized, is accompanied by limited information regarding their toxicity. In some cases, uremic abnormalities have been reproduced by the transfer of uremic serum or plasma to normal animals or cells (Table 18-2). But the role of particular solutes in causing these abnormalities remains uncertain.

Solutes Cleared By the Kidney and Retained in Uremia

The long list of solutes retained in uremia has been assembled in two ways. Initially, biochemists would find a substance in the urine and then look for it in the blood of uremic patients. Several dozen uremic solutes were identified in this way as the biochemical pathways of intermediary metabolism were worked out. Beginning about 1970, improved analytic techniques, including gas chromatography, mass spectroscopy, and high-performance liquid chromatography, were used to identify numerous additional uremic solutes.[4] Often, the new methods identified compounds that were structurally related to a previously known uremic solute but present in lower concentrations. For example, the tryptophan degradation product indoxyl sulfate was identified in the urine in the late nineteenth century and shown to accumulate in the blood of uremic patients in 1911. Several other indoles had been shown to accumulate in uremia by 1970, and the subsequent application of high-performance liquid chromatography led to the identification of additional substances.

Recent technical advances, including the development of proteomic and metabolomic screening techniques, will undoubtedly lengthen the list of uremic solutes. But the problem remains of determining which solutes are toxic. In general, the compounds that are present in the highest concentrations, and were therefore first identified, have been studied most. Plasma concentrations of several compounds have been shown to correlate more closely with uremic symptoms, and, in particular, with altered mental function, than concentrations of urea or creatinine. In some cases, these compounds have been shown to accumulate in the cerebrospinal fluid consistent with their proposed effect on the brain. But experiments showing that uremic signs and symptoms can be replicated by raising solute levels in normal people or animals to equal those observed in uremic patients are lacking. When attempted, such experiments have generally shown that the solutes being studied are more toxic than urea, but that the levels required to produce toxic effects are higher than those measured in patients. Because so little is known about their toxicity, the discussion of uremic solutes is usually organized on the basis of their structure and not on their contribution to disease.

Individual Uremic Solutes

Urea Urea is quantitatively the most important solute excreted by the kidney, and levels rise higher than those of any other solute when the kidney fails. But early studies indicated that urea causes only a minor part of uremic illness.[5–7] In the most often cited of these studies, Johnson and colleagues[6] dialyzed three patients with renal failure against bath solutions containing urea. They found that initiation of hemodialysis improved uremic symptoms, including weakness, fetor, and gastrointestinal upset, even when the blood urea nitrogen (BUN) was maintained at approximately 90 mg/dl. In patients already on dialysis, increasing the BUN to 140 mg/dl did not cause recurrence of uremic symptoms. Increasing the BUN above 140 mg/dl caused nausea and headaches, and increasing the BUN above 180 mg/dl caused weakness and lethargy. But symptoms in dialyzed patients whose BUN values were increased to these levels were felt to be much less severe than symptoms in undialyzed patients with similar BUN values. Studies in patients without renal failure further suggest that urea by itself does not cause uremia. Uremic symptoms have not been observed in patients in whom BUN levels are maintained at approximately 60 mg/dl by high protein intake or increased tubular urea absorption.[8–10]

The finding that uremia is not replicated by an isolated elevation of the urea level does not mean that urea has no toxic effects.[11] The full expression of uremia may require the accumulation of urea plus other solutes. Johnson and colleagues[6] noted that patients dialyzed against solutions of urea exhibited increased bleeding, and subsequent studies have suggested that urea causes bleeding by promoting synthesis of guanidinosuccinic acid, which, in turn, impairs

platelet function.[12,13] Increased urea levels may cause other ill effects by promoting protein carbamylation.[14] Isocyanate, which forms spontaneously at a rate proportional to the urea concentration, combines irreversibly with unprotected amino groups to form carbamylated proteins (Figure 18-1). This process can be considered analogous to the formation of glycated proteins in diabetes, and measurement of hemoglobin carbamylation provides an index of the time-averaged urea concentration.[15] Isocyanate can also combine reversibly with OH and SH groups of amino acids, and the various isocyanate induced alterations in structure could impair protein function.

A further potential consequence of increased urea levels is increased ammonia production. Each day colonic bacteria transform a portion of the body urea pool to ammonia, which is then taken up by the liver and either converted back to urea or incorporated into amino acids.[16,17] Surprisingly, the flux through this pathway appears not to increase as urea levels rise in patients with renal failure, and gut ammonia synthesis and blood ammonia levels remain normal.[17] Recent studies, however, have found that breath ammonia levels are markedly elevated in hemodialysis patients and fall during treatment.[18,19] Why breath ammonia levels are elevated while blood ammonia levels remain normal is unexplained.

D-Amino Acids In comparison to urea, we know much less about most other potential uremic toxins. The d-amino acids exemplify this problem. Aggregate plasma levels of d-amino acids increase as kidney function declines,[20,21] but the

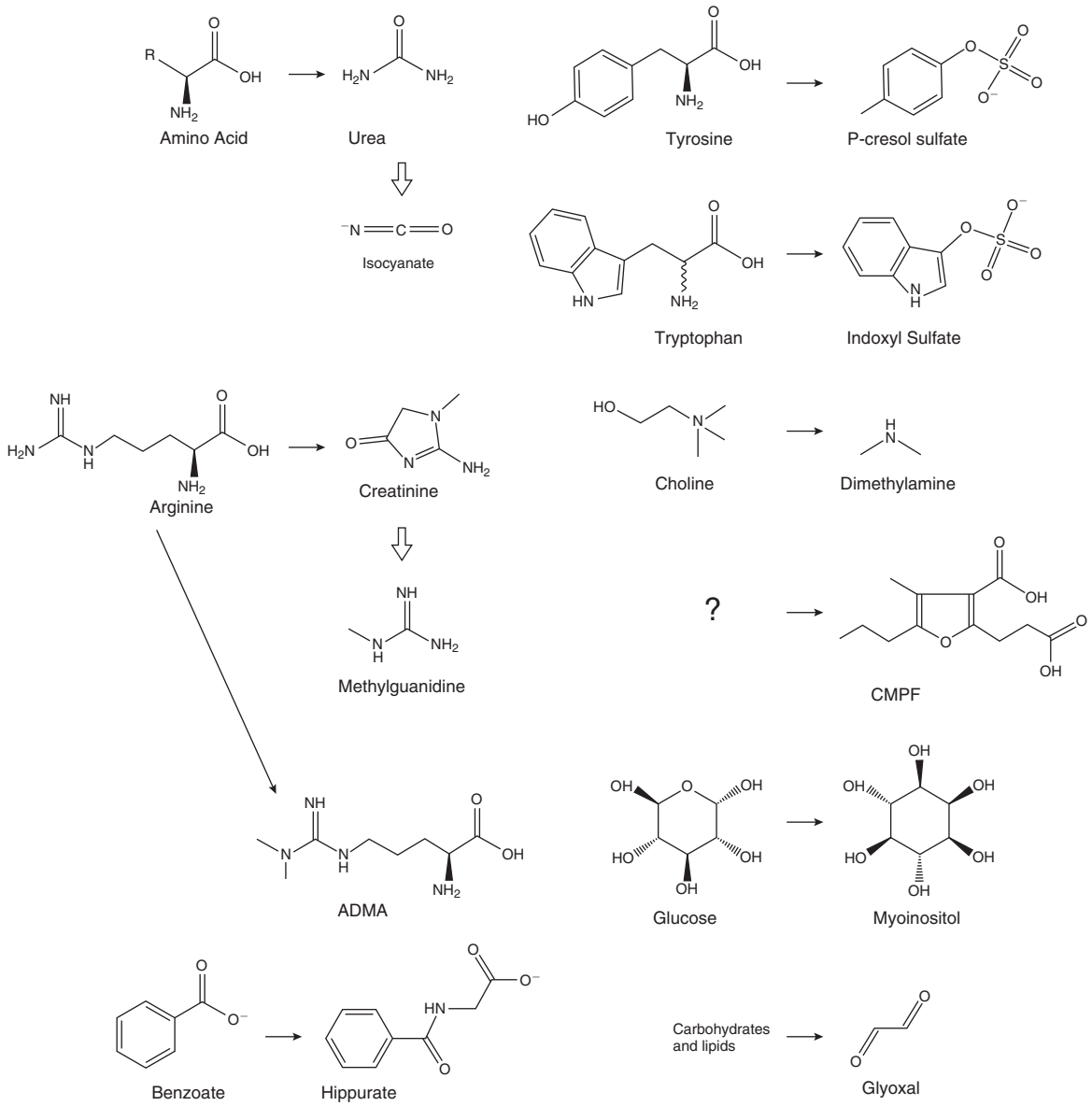


FIGURE 18-1 The generation of potential uremic toxins. The substances in the right column of each panel are metabolites that are normally excreted by the kidney and therefore accumulate in the extracellular fluid when kidney function is lost. The left column shows the substances from which these potential "*uremic toxins*" are derived. In some cases, the biochemical derivation of the potential toxins is uncertain. For instance, it is not known what fraction of the dimethylamine normally excreted is derived from choline and the source of CMPF is obscure. See text for details.

source, clearance, and toxicity of the d-amino acids found in the plasma are not well-defined. Recent studies have shown that d-amino acids can be synthesized by mammalian cells and derived from food and produced by colonic bacteria.[22] Circulating d-amino acids are filtered by the glomerulus and then in varying proportion reabsorbed intact, degraded by d-amino acid oxidase (DAO) or d-aspartic acid oxidase in the proximal straight tubule, or excreted unaltered in the urine.[23,24] The liver can also clear d-amino acids, and the relative importance of renal and hepatic clearance is not known. Aggregate d-amino acid levels have been found to increase almost in proportion to the serum creatinine in renal failure, suggesting that renal clearance predominates.[20,25,26] But levels of individual d-amino acids measured so far, including d-serine increase less than the creatinine.[25,26] This discrepancy remains unexplained. It is tempting to speculate that d-amino acids are cleared rapidly from the ECF because they have toxic effects. It has long been presumed that high levels of d-amino acids could impair protein synthesis or function.[22] D-amino acid accumulation could also interfere with the recently identified effects of endogenous d-serine and d-alanine on neuronal function.[27] No major ill effects of d-amino acid accumulation have been observed in DAO deficient mice, which have higher d-amino acid levels than humans with renal insufficiency.[28,29] Exogenous d-amino acids have so far been shown to be toxic when administered in large quantities only.[28,30]

Peptides and Proteins The kidney clears circulating dipeptides and tripeptides, which may comprise a significant portion of the extracellular amino acid pool.[31] Filtered dipeptides and tripeptides can be broken down by brush border peptidases and reabsorbed as amino acids or reabsorbed by a brush border peptide transporter and then hydrolyzed within proximal tubule cells.[32] Peritubular uptake, again followed by hydrolysis to amino acids, makes the renal clearance of many peptides greater than the glomerular filtration rate (GFR).[31,33] Small peptides are also taken up by other organs and generally do not accumulate in renal failure. Peptides containing altered amino acids, which are normally cleared by the kidney, may be an exception to this rule.[33]

The kidney plays a proportionally greater role in the clearance of larger peptides. Proteins with molecular weight 10–20 kD such as ß2 microglobulin and cystatin C are normally filtered by the glomerulus and then endocytosed and hydrolyzed in the lysosomes of proximal tubular cells.[34,35] Their plasma levels therefore rise in close proportion to the plasma creatinine as the kidney fails. Indeed the plasma concentration of cystatin C, which is released at a near constant rate by nucleated cells, may provide a better measure of the GFR than the concentration of creatinine. The role of the kidney in the removal of peptides with molecular weight between 500 D and 10 kD is less well-defined. Peptides in this range are also filtered by the glomerulus and then either hydrolyzed by brush border peptidases or endocytosed, depending on their size and structure. Biologically, active peptides such as insulin may also be cleared by peritubular uptake. Studies in patients with inherited dysfunction of proximal tubular endocytosis suggest that the normal kidney clears approximately 350 mg/day of peptides with molecular weight 5–10 kD from the circulation.[36] The relative importance of renal to extrarenal clearance has not been defined for most substances in this size range. The extent to which circulating levels of such peptides are increased in renal failure is therefore unpredictable. Even less is known about the kidney's contribution to the clearance of peptides in the range of 500 D to 5kD. But the summed level of peptides and small protein concentrations in the plasma of uremic patients have been estimated to be approximately 50 mg/L.[37]

Although the aggregate peptide levels in renal failure remain ill-defined, we have some knowledge of individual retained substances. These include protein degradation products like the C-terminal fragments of the parathyroid hormone and intact small proteins like cystatin C. The middle molecule hypothesis stimulated early workers to isolate and sequence a few peptides from uremic serum. Proteomic techniques are now being applied and will hopefully yield a fuller picture.[38,39] One study suggests that the bulk of retained peptides with molecular weight 500 D to 5 kD are fibrinogen fragments.[39] Another study has identified more than 1000 peptides with molecular weight from 800 D to 10 kD in the plasma of dialysis patients.[40] The central question, of course, is whether any of these substances are toxic. It has been widely speculated that retained peptides can cause inappropriate activation of various hormone or cytokine receptors. For example, retained complement protein D (mw 24kD) could contribute to systemic inflammation and excess vascular disease in dialysis patients.[41] Such hypotheses remain largely unproven, however, and ß2 microglobulin is the only retained peptide that has been convincingly shown to cause disease.

Guanidines Among the compounds most frequently considered uremic toxins are guanidines, which, like urea, are derived from arginine (see Figure 18-1).[42,43] One group of guanidines that accumulate in uremia includes creatinine and its breakdown products. Creatinine is produced by nonenzymatic degradation of creatine, which, in turn, is made from guanidinoacetic acid (GAA).[44] Creatinine itself appears not to be toxic, and levels have been increased transiently to more than 100 mg/dl in subjects undergoing clearance studies. Interest has been focused rather on the potential toxicity of various creatinine metabolites, including particularly creatol and methylguanidine.[45,46] The production of these substances increases as creatinine levels rise and may be stimulated by increased levels of intracellular oxidants.[43–45] Methylguanidine is also produced by colonic bacteria, and its production may be increased by increasing the dietary intake of protein or creatinine.[47] Another guanidine that has attracted interest is guanidinosuccinic acid (GSA), which is formed not from creatinine but from the urea cycle intermediate arginosuccinate.[48,49] Rising urea levels impede the conversion of arginosuccinate to urea and increase the production of GSA. The production of GSA thus depends on dietary protein intake and on renal function and may in renal insufficiency also be stimulated by increased levels of intracellular oxidants.[49,50]

Creatol, methylguanidine, and GSA share the interesting property that their plasma levels rise out of proportion to urea and creatinine levels as the GFR falls. This is because they are cleared largely by glomerular filtration, and their production increases as creatinine and urea levels rise.[43–45] In addition, large volumes of distribution combined with restricted intercompartmental diffusion may limit the

removal of creatol, methylguanidine, and GSA by hemodialysis.[42] In patients receiving conventional intermittent treatment, these compounds therefore exhibit the highest concentrations relative to normal of the known uremic solutes.[1] The finding that they are present in relatively high concentrations of course does not prove that they are toxic, but the evidence for the toxicity of various guanidines, although incomplete, is stronger than that for most other solutes. Administration of methylguanidine aggravates uremic symptoms in dogs, whereas GSA contributes to uremic platelet dysfunction, and a number of guanidines impair neutrophil function.[12,51,52] In addition, various guanidines have been shown to accumulate in the brain and CSF in uremia and may contribute to central nervous system (CNS) dysfunction.[53]

The methylated arginines, asymmetrical dimethyl arginine (ADMA) and symmetrical dimethyl arginine (SDMA) also accumulate in renal failure (see Figure 18-1). But their metabolism is quite different from that of the other "*uremic*" guanidines. ADMA and SDMA are formed by methylation of arginine residues in nuclear proteins and are released when these proteins are degraded. Interest has focused largely on ADMA because it inhibits nitric oxide synthesis, whereas SDMA is relatively inactive.[54,55] The kidney clears ADMA at a rate approximating the creatinine clearance, but the majority of plasma ADMA is taken up and degraded intracellularly at other sites.[54] The increase in ADMA levels observed in patients with renal insufficiency is therefore generally attributed to a reduction in extrarenal clearance, as an increase in their production has not been observed. The mechanism responsible for reducing the extrarenal clearance of ADMA in renal disease is not known, but it is remarkable that ADMA levels may rise to approximately twice normal very early in the course of renal disease and then not increase much further as patients advance to ESRD.[56] Increases in ADMA levels, although modest in proportion to increases in the levels of other uremic solutes, have been associated with accelerated progression of renal injury and an increased risk for cardiovascular disease and death in patients with renal disease.[57]

Phenols and Other Aromatic Compounds Phenols are compounds having one or more hydroxyl groups attached to a benzene ring. In discussions of uremia, phenols are usually considered together with other aromatic compounds such as hippurates, and the term *phenols* is sometimes used loosely to include these other substances. The aromatic compounds normally found in the ECF are for the most part derived either from the amino acids tyrosine and phenylalanine or from aromatic compounds contained in vegetable foods. Medications provide an additional source in patients. The compounds in the ECF are mostly metabolites, derived from their parent compounds by a combination of methylation, dehydroxylation, oxidation, reduction, and/or conjugation. Many of these reactions take place in colonic bacteria. The final step, which is usually conjugation with sulfate, glucuronic acid, or an amino acid may take place in the liver, the intestinal wall or, to a lesser extent, the kidney.[58,59] In general, conjugation tends to make the aromatic compounds at once less toxic and more polar, which facilitates their excretion by various organic ion transport systems.

The metabolic processes described previously produce a bewildering array of aromatic compounds that are normally excreted in either the urine or the feces. The aggregate urinary excretion of aromatics is on the order of 1000 mg/day and varies widely with the diet. The compounds normally excreted by the kidney accumulate in uremia and contribute to the elevation of the anion gap because the majority of aromatic conjugates are negatively charged.[60] Levels of individual compounds in uremic patients range from barely detectable up to 500 M.[1,61–63] The relatively few compounds that have been studied extensively, including the examples described below, are among those found in the highest concentrations. There is no reason to think that the compounds found in the highest concentrations are the most toxic. Interest in the contribution of phenols and other aromatic compounds to uremic toxicity has been encouraged by reports that uremic symptoms are better correlated with levels of these compounds than with levels of other solutes,[7,64–66] but evidence so far obtained for the toxicity of individual aromatic compounds is not strong.

The most extensively studied aromatic uremic solute is hippurate (see Figure 18-1). Because it is the aromatic waste compound normally excreted in the largest quantity, its free level rises higher than those of other aromatic solutes in the plasma of uremic patients. Hippurate is the glycine conjugate of benzoate, which is derived largely from vegetable foods with only a small amount formed endogenously from the amino acid phenylalanine.[67,68] Diet therefore determines hippurate production, and hippurate excretion in aboriginal people eating vegetable diets may exceed hippurate excretion in people from industrialized nations by many fold.[69] In people with normal kidneys, active tubular secretion keeps hippurate levels much lower than they would be if hippurate were cleared solely by glomerular filtration. Hippurate, however, is not toxic. Hippurate levels in normal humans can be increased to equal those of uremic patients without apparent ill effect.[70] Increasing hippurate levels by benzoate feeding in patients with renal failure does not aggravate uremic symptoms.[71]

Another extensively studied aromatic compound is p-cresol. In contrast to hippurate, which is derived from aromatic compounds in plants, p-cresol is formed by the action of colonic bacteria on tyrosine and phenylalanine. The portion of amino acids that escape absorption in the small intestine may be increased in uremic patients, leading to increased production of p-cresol and other bacterial metabolites.[72] P-cresol binds avidly to serum albumin, and the effect of different renal replacement therapies on albumin-bound solutes has often been tested by measuring p-cresol levels.[73,74] Unconjugated p-cresol is toxic.[75] Higher levels of free serum p-cresol have been prospectively associated with mortality and cardiovascular events in a Belgian hemodialysis cohort.[66,76] But p-cresol circulates almost exclusively as p-cresol sulfate, which is much less toxic, and reports of unconjugated p-cresol in the plasma of uremic patients now appear to have been the result of inadvertent hydrolysis of p-cresol sulfate during the processing of plasma samples.[77–79]

Other aromatic uremic solutes have been identified in great numbers but studied less extensively.[2,62,63] Metabolites of tyrosine and phenylalanine that accumulate in uremia include phenylacetylglutamate, parahydroxyphenylacetic acid, 3,4 dihydroxybenzoic acid, and p-cresol.[80–82] The structural relation of these aromatic amino acid metabolites to

neurotransmitters has stimulated interest in their potential role as uremic toxins. So far, 3,4 dihydroxybenzoate has been shown to cause CNS dysfunction in rats, but only at levels higher than those encountered in uremic patients.[81] The work of testing the toxicity of other aromatic uremic solutes is daunting, and little progress has been made.[2]

Indoles and Other Tryptophan Metabolites Indoles are compounds containing a benzene ring fused to a five-membered nitrogen containing pyrrole ring (see Figure 18-1). Many similarities are encountered in considering the indoles and phenols in uremia. As with the phenols, some indoles are derived from plant foods and others are produced endogenously, but the endogenous indoles are derived mostly from tryptophan, whereas the phenols are derived from phenylalanine and tyrosine. As with the phenols, minor chemical modifications in various combinations yield a remarkable variety of structures, with more than 600 indoles derived from tryptophan.[83] Those with known physiological function include the neurotransmitter 5-hydroxytryptamine (serotonin) and melatonin. Other indoles are considered to be waste products and are often conjugated before urinary excretion. These uremic indoles accumulate in the extracellular fluid when renal function is reduced.

The most extensively studied of the uremic indoles is indoxyl sulfate, or indican. Indican is produced from tryptophan in a manner reminiscent of the production of p-cresol sulfate from tyrosine and phenylalanine. Gut bacteria convert tryptophan to indole, which is then oxidized to indoxyl and conjugated with sulfate in the liver. There is evidence that indican is toxic in vitro, but early studies of indican infusion failed to replicate uremic symptoms.[7,84] Like p-cresol sulfate, indican is extensively bound to serum albumin, and recent studies have employed it as a marker of the removal of protein bound solutes by renal replacement therapies.[74]

It has been suggested that indican is toxic to renal tubular cells and that increasing indican levels accelerate the loss of remnant nephrons in kidneys that have been damaged by disease.[85] In an in vitro model indican induced oxidative stress in endothelial cells via increased NADPH oxidase activity and reduced intracellular glutathione levels.[86] Orally administered indoxyl sulfate reduced superoxide scavenging activity in the kidneys of normal and subtotally nephrectomized rats.[87] It worsened renal function in the latter, providing further evidence of its potential role as a nephrotoxin impairing antioxidant systems in the kidney. Treatment of rats with the oral adsorbent AST-120 after subtotal nephrectomy reduced levels of indican and oxidized serum albumin, a sensitive marker of oxidative stress.[88] It further slowed the loss of renal function compared to nontreated rats. Indican stimulates vascular smooth muscle cell proliferation in vitro.[89] Inhibition of organic anion transporter 3 (OAT3) blocks this effect, suggesting that indican is at least partly taken up into vascular smooth muscle through OAT3. High levels of indican were associated with markers of cardiovascular disease in 224 prevalent hemodialysis patients, including higher levels of the advanced glycation end product (AGE) pentosidine and lower high-density lipoprotein (HDL) levels.[90] Finally, in a randomized, double-blind, placebo-controlled trial in patients with moderate to severe CKD, AST-120 was associated with lower indican levels and improvements in malaise in a dose-dependent fashion.[91]

Other indoles that accumulate in uremia include indoleacetic acid, indoleacrylic acid, and 5-hyroxyindoleacetic acid.[1,92,93] As with the phenols, the indoles are structurally related to potent neuroactive substances, which in the case of the indoles include serotonin and LSD. This structural similarity has stimulated interest in their potential role as neurotoxins, but few uremic indoles have so far been administered to normal animals, and none have convincingly been shown to alter CNS function at the levels encountered in uremic patients.

Only a minor portion of dietary tryptophan is excreted as indoles. Most is metabolized by the kynurenine pathway that allows tryptophan to be converted to glutarate and oxidized or, when necessary, used in the synthesis of nicotinamide. Renal failure causes members of the kynurenine pathway including l-kynurenine and quinolinic acid to accumulate in the plasma.[94,95] Knowledge that these substances play a physiological role in the modulation of CNS function has stimulated interest in their possible contribution to uremic toxicity. As usual, however, evidence that they are toxic at the levels encountered in uremic patients has not been obtained.

Aliphatic Amines The methylamines monomethylamine (MMA), dimethylamine (DMA), and trimethylamine (TMA) are among the simplest compounds that have been considered to be uremic toxins. Early studies identified high levels of DMA and TMA in patients with impaired renal function, and subsequent studies reported a more than 10-fold rise in serum concentrations for both DMA and MMA in people with ESRD compared to controls.[96,97] However, available data and predictions based on their chemistry suggest that the methylamines are poorly removed by dialysis, and limited data suggest that they may even be produced in excess in uremia.

A large volume of distribution may contribute to poor removal of the methylamines by dialysis. These compounds are bases with pKs ranging from 9–11. Thus, they exist as positively charged species at physiological pH. The lower intracellular pH compared to extracellular should lead to their preferential intracellular sequestration with volumes of distribution exceeding total body water. Indeed, measurements in experimental animals and humans have confirmed these predictions for DMA and TMA.[98,99]

Because they circulate as small organic compounds that are not protein bound, these three amines are likely freely filtered. However, because they exist as organic cations, they also have the potential to be secreted by one or another of the family of organic cation transporters.[100] Hence, they may achieve clearances that are in fact greater than the GFR. The chemically similar exogenous compound, tetraethyl ammonium, has long been a prototype test solute for organic cation secretion and is cleared at rates up to (and in one study, above) the renal plasma flow.[101,102] Although formal renal clearances of MMA, DMA, and TMA are not available, the total metabolic clearances of DMA and TMA by plasma disappearance of labeled compounds in rats approach that of renal plasma flow.[98]

The biochemical pathways leading to MMA, DMA and TMA are not well-delineated. Both the host's mammalian tissues and resident gut flora seem to contribute to the net appearance of these amines. The dietary precursors for MMA, DMA, and TMA include choline and trimethylamine oxide (TMAO).[103–105] Production of these compounds may actually be increased with uremia because of overgrowth of intestinal bacteria.[99,106] Thus suggestive data

support the possibility that in the patient with ESRD, production may be increased in the face of impaired renal removal.

Incomplete data also implicate the amines as toxic.[107] Their levels were found to correlate better than creatinine with impairment of brain function as manifest by EEG and cognitive testing.[108] Perhaps more telling but less quantitative was the association between falls in amine levels and clinical improvement in myoclonus, asterixis, and mental acuity when non-absorbable antibiotics were administered orally, even without dialysis and hence without change in serum urea or creatinine.[109] This effect was attributed to suppression of the overgrowth of intestinal flora that produces these aliphatic amines. Other toxicities have been assigned to this class of amines as well. MMA may be the most toxic and its effects include a variety of neural toxicities, hemolysis, and inhibition of lysosomal function.[110] The uremic fetor or fishy breath noted in uremic patients is attributable to TMA.[111] While the malodor may be of no major consequence in itself, the potentially important and well-described diminutions in taste and smell among these patients may also be related to the amines. More recently two additional adverse actions have come to light. MMA is a potent anorectic agent when administered into the cerebrospinal fluid in mice and at levels that are similar to those reported in plasma of patients with ESRD.[112–114] Also the potential toxicities of MMA's oxidation products via the enzyme SSAO—hydrogen peroxide and formaldehyde—may injure blood vessels, which are a major site of SSAO activity.[115]

3-Carboxy-4-Methyl-5-Prophy-2-Furanpropanoic Acid The literature on 3-carboxy-4-methyl-5-prophy-2-furanpropanoic acid (CMPF) further illustrates many of the difficulties encountered in the study of uremic solutes. CMPF was identified in the urine more than 25 years ago. It was subsequently shown to accumulate in the plasma as renal function is lost and to bind so tightly to albumin that it is scarcely removed by conventional hemodialysis.[74,116] It has attracted interest because its occupation of albumin binding sites contributes to the reduced binding of both other endogenous solutes and drugs in uremic patients,[117,118] Its biochemical source, rate of production, and routes of clearance in both normal subjects and uremic patients remain to be defined. Wide variation in the levels reported in uremic patients further suggest that there are unrecognized differences among assay methods for CMPF. It has been hypothesized that CMPF causes neurotoxicity by interfering with the transport systems that remove toxic organic molecules from the cerebrospinal fluid.[119] But investigation has proceeded slowly without stronger evidence of toxicity. Other furancarboxylic acids also accumulate in uremia but in much lower concentrations.[117]

Myoinositol and Other Polyols Plasma concentrations of a number of polyols increase in uremia. The compound that is found in the highest concentration and has been studied most extensively is myoinositol (see Figure 18-1).[120,121] Myoinositol is different from most other uremic solutes in that it is normally oxidized by the kidney. Its accumulation in uremia therefore reflects impaired degradation and not impaired excretion. The amount of myoinositol excreted in the urine actually increases along with the plasma level as less myoinositol is degraded by failing kidneys.[121] Early studies of myoinositol focused on its potential contribution to uremic polyneuropathy, but evidence that myoinositol causes nerve damage, although stronger than most of the evidence for the toxicity of uremic solutes, is far from conclusive.[122] Other polyols including mannitol, sorbitol, arabitol, and erythritol accumulate in uremia to a lesser degree.[120,121] They are commonly discussed together with myoinositol, but do not have similarly important roles in normal phospholipid metabolism and have not been considered significant contributors to uremic toxicity.

Other Uremic Solutes The purine metabolite uric acid is the only organic substance whose plasma level is known to be actively regulated by variation of its renal excretion. When renal failure is advanced, the capacity of the kidney to increase the fractional excretion of uric acid is exceeded, and uric acid levels increase along with those of its precursor molecules xanthine and hypoxanthine. Other nucleic acid metabolites excreted by the kidney are produced in much lesser quantities. Many are derived from the modified nucleosides contained in tRNAs.[123] They appear to be cleared largely by filtration and to accumulate in the plasma as the GFR falls. It has been suggested that pseudouridine, which is the most abundant of these substances, contributes to insulin resistance and altered CNS development, but, as usual, the demonstration of its toxicity is not conclusive.[123,124]

Oxalate is also excreted by the kidney and accumulates in renal failure. The plasma concentration of oxalate, which is derived from plant foods and from endogenous catabolism of substances including vitamin C, varies widely.[125,126] Very high levels have been found in patients consuming oxalate rich diets and taking vitamin C, and deposition of calcium oxalate in skin, heart, and other tissues has been observed in some cases.

A number of studies have identified abnormal polyamine levels in uremia, though there is not clear reason why renal failure should affect the metabolism of these largely intracellular substances. Early studies suggested that levels of putrescine, cadaverine, spermidine, and spermine were elevated in patients with renal failure, and several studies suggested that accumulation of polyamines was responsible for reduced erythropoesis.[2,127] More recent studies have found that plasma levels of spermidine and spermine are decreased in patients with renal failure while levels of putrescine are only moderately elevated.[128] The focus of these latter studies has been on the hypothesis that accumulation of acrolein produced during the degradation of polyamines leads to the production of modified proteins.

Additional substances excreted by the kidney that accumulate in renal failure include various pteridines and dicarboxylic acids.[123,129,130] The list of uremic solutes is lengthening as improved analytic methods identify solutes present in low concentration. The possibility of toxicity is invariably considered when new solutes are identified, but experiments to test the toxicity of uremic solutes are now rarely performed.

Solute Removal by Different Forms of Renal Replacement Therapy

Although investigators have not succeeded in replicating uremic illness by administering uremic solutes to normal humans or animals, reversing illness by removing solutes has become a part of everyday practice. The difficulty is that renal replacement therapies remove solutes indiscriminately,

so that the improvement they effect cannot be attributed to removal of any individual compound. Different forms of renal replacement therapy do, however, clear solutes at different rates based on characteristics including molecular size, protein-binding, and sequestration within cells or other body compartments. The demonstration that different therapies have different effects on some feature of uremic illness might therefore reveal the properties of the responsible toxin.

The Original Middle-Molecule Hypothesis

The suggestion that the nature of uremic toxins could be deduced by comparing the effect of different renal replacement methods was first advanced by Scribner and Babb and their colleagues.[131] In the 1960s, hemodialysis was performed with membranes that provided very limited clearance of solutes with molecular weight less than 1000 D. Treatment with these membranes wakened patients from coma, relieved vomiting, and partially reversed other uremic symptoms. This provided evidence, which remains convincing, that some important uremic toxins are small. But Scribner and his associates were impressed that patients on peritoneal dialysis were healthier than patients on hemodialysis who had the same urea and creatinine concentrations. They further observed that increasing the dialysis duration from 6.5 to 9 hours three times weekly prevented neuropathy. These observations led them to conclude that important toxins were larger than 300 D because, as compared to contemporary hemodialysis membranes, the peritoneal membrane afforded greater relative permeability in this size range, and because increasing the dialysis duration was expected to reduce the concentration of large molecules more than the concentration of creatinine and urea. Based on their further impression that no additional benefit was obtained using membranes that provided superior clearance for solutes with size greater than 2000 D, they concluded that some important toxins were "*middle molecules*" with molecular weight greater than 300 D but less than 2000 D.[132]

Large Solutes—the Changing Definition of "*Middle Molecules*"

Only equivocal evidence was obtained during the 1970s that increasing the clearance of solutes with molecular weight between 350 D and 2000 D improved the health of uremic patients.[131] The proposition that no benefit could be obtained by increasing the clearance of solutes with molecular weight greater than 2,000 D was never prospectively tested. The original "*middle molecule hypothesis*" was thus never proven to be correct. Although the term "*middle molecules*" remains in use, its meaning has gradually shifted to include larger solutes. The 2003 report of the European Uremic Toxin Work Group[1] thus defined middle molecules as having a size greater than 500 D and less than 60,000 D, which is nearly the size of albumin. In practice, the adoption of new membrane materials, which was in part a response to the original "*middle molecule hypothesis*," has ended investigation of the relative toxicity of solutes that fall in different parts of the size range less than 1000 D. The question of whether solutes with molecular weight greater than 1000 D exert toxic effects remains under investigation. Henderson and colleagues[133] showed that such solutes can be cleared more effectively by hemofiltration than by hemodialysis. Although maintenance hemofiltration has been practiced on a small scale for many years, its benefit as compared to hemodialysis remains to be established. Increasing large solute clearances to the extent that this can be accomplished by hemodialysis using "*high flux*" as compared to "*low flux*" membranes was not found to have any benefit in the HEMO study.[134] Practically all of the known examples of solutes with size greater than 1000 D are peptides. The only one so far proven to be toxic, and indeed the one that has been extensively studied, is ß$_2$ microglobulin that has a molecular weight of approximately 12,500 D. It should be noted that even when "*high flux*" membranes are used clearances of large solutes obtained by hemodialysis are much lower, in comparison to the clearance provided by the normal kidney, than the clearances of urea and creatinine. For ß$_2$ microglobulin, the reduction in plasma levels obtained by shifting from low flux to high flux membranes is modest, further suggesting that most of its clearance is accomplished by means other than dialysis.[135] Studies that achieve higher clearances of large solutes and include solutes other than ß$_2$ microglobulin are required to assess the contribution of large solutes to uremic illness.

Protein-Bound Solutes

Another group of solutes that are poorly removed by standard hemodialysis includes those that bind to albumin.[3,74,75,136] Their dialytic clearance is low not because they are large molecules, but because only the free, unbound solute concentration contributes to the gradient driving solute across the dialysis membrane. When expressed as multiples of normal, levels of these compounds are therefore much higher than levels of unbound solutes like urea and creatinine in hemodialysis patients.[75]

Small solutes bind competitively to albumin at a number of sites.[137] One effect of the aggregate accumulation of protein-bound solutes in uremia is to decrease the binding of individual substances.[138] Thus uremic patients exhibit an increase in the unbound fractions of the amino acid tryptophan and of drugs including phenytoin, furosemide, salicylate, and many others. The decreased drug binding observed in uremic plasma has so far not been fully replicated by addition of known uremic solutes to normal plasma, and our current list of the protein-bound solutes that accumulate in uremia is undoubtedly incomplete.[139] But there is reason to suspect that at least some of the protein-bound solutes that accumulate in uremia are toxic. The normal kidney achieves high clearance rates for many protein-bound solutes by active tubular secretion. Presumably, the combination of protein-binding and tubular secretion represents an evolutionary adaptation that allows for excretion of toxic molecules while keeping their concentrations in the extracellular fluid very low.[101]

In vitro evidence has been obtained for the toxicity of some protein-bound solutes, but, as usual, this evidence is not conclusive.[119] The aggregate toxicity of protein-bound solutes could theoretically be assessed by comparing the effect of different renal replacement prescriptions, but this has not been attempted in practice. Mathematical models predict that hemofiltration, which removes large solutes more effectively than routine hemodialysis, removes protein-bound

solutes less effectively.[140] But clinical studies to test this prediction have not been performed. Addition of a sorbent to the dialysate improves the clearance of protein-bound solutes. The maximal effect of addition of a sorbent is equivalent to an unlimited increase in dialysate flow.[141] Fractionated plasma separation and adsorption, developed for the treatment of liver failure, improved the clearance of p-cresol sulfate compared to high-flux hemodialysis; however, this study was halted as three of the four participants developed thrombosis of their arteriovenous access.[142] Recent studies have shown that peritoneal dialysis clears protein-bound solutes at a very low rate, and that removal of protein-bound solutes in patients maintained on peritoneal dialysis depends heavily on residual renal function.[143] Yet contrary to expectation, levels of indican and p-cresol sulfate do not markedly rise in peritoneal dialysis patients without residual function, probably because of reduced production in these individuals.[144]

Sequestered Solutes

Some solutes are sequestered or held in compartments where their concentration does not equilibrate rapidly with that of the plasma.[145] Application of a high dialytic clearance may rapidly lower the plasma concentration of such solutes while removing only a small portion of the total body content. When this happens, intermittent dialysis treatment will be followed by a rebound in the plasma solute concentration toward predialysis levels.

The effect of sequestration on the removal of urea, which is generally used to assess dialysis adequacy, is modest.[3] It is widely assumed that many organic solutes equilibrate more slowly than urea between compartments such as cell water and the plasma. Studies demonstrating sequestration of creatinine, uric acid, and several guanidines are consistent with this assumption, but the behavior of other solutes has not been examined.[42,146,147] Theoretically, the contribution of sequestered solutes to uremic toxicity, like the contribution of large solutes or protein-bound solutes, could be assessed by comparing the efficacy of different dialysis prescriptions. When treatment is intermittent, the removal of sequestered as compared to freely equilibrating solutes can be increased by lengthening the treatment while reducing the plasma clearance. It has been suggested that this effect may be responsible in part for the exceptional results reported with slow thrice weekly hemodialysis.[148] But available studies are not sufficiently well-controlled to confirm the importance of sequestered solutes.

Effects of Diet and Gastrointestinal Function

It may be possible to identify uremic toxins by comparing the effects of different diets and different renal replacement therapies. Patients with renal failure tend to spontaneously reduce their intake of protein.[149] Before dialysis became available, physicians found that the protein restriction relieved uremic symptoms.[150] These findings suggest that important uremic toxins are derived from protein catabolism. Uremic solutes whose production has been shown to depend on protein intake include urea, methylguanidine, GSA, and the indoles and phenols that are produced by the action of gut bacteria on tryptophan, phenylalanine, and tyrosine.[50,61,151–153] The dependence of most other solutes on dietary protein is unknown, and the effect of the intake of individual amino acids on uremic solute production has not been studied. It seems likely that uremic toxins can also be derived from other dietary constituents and that uremic patients may have limited tolerance for certain foods just as they have limited tolerance for certain medications. Dialysis patients have become comatose following ingestion of star fruit, a member of the *Oxalidaceae* family.[11] Given the variety of chemicals contained in plants, there are remarkably few reports of this kind.[154]

The production of uremic toxins may depend not only on dietary intake, but also on gut function. Uremic solutes made by colonic bacteria include methylamines and some indoles and phenols.[111] The production of these compounds in uremic patients may be increased by impaired small bowel function, which increases delivery of their precursors to colonic bacteria, or by the penetration of colonic bacteria into the ileum.[106,155] If colonic bacteria produce uremic toxins, uremic symptoms could theoretically be relieved by reducing colonic transit time or by altering the colonic flora, but only limited studies of such maneuvers have so far been performed.[109,156]

Solute Excretion by Tubular Transport Systems

The cloning of transporters that move organic solutes into the lumen of the proximal tubule has provided a possible new route to the identification of uremic toxins. To the extent that uremia is caused by accumulation of organic solutes, knocking out these transporters would be expected to reproduce uremic symptoms. To date, knocking out both the organic cation transporters 1 and 2 has been shown to abolish tubular secretion of organic cations without causing detectable illness.[157] Similarly, mice in which the organic anion transporter 1 has been knocked out exhibit a reduced clearance for para aminohippurate and other organic anions but otherwise appear normal.[158] Redundancy of the transport mechanisms for important toxins and the residual clearance provided by glomerular filtration may limit the effects of deleting transport molecules.

METABOLIC EFFECTS OF UREMIA

The loss of renal function has numerous metabolic effects. A few of these can be related to the loss of specific renal processes such as the hydroxylation of vitamin D, but most have no clear cause and can at present be attributed to the retention of uremic solutes only.

Oxidant Stress and the Modification of Protein Structure

Recent studies suggest that loss of kidney function increases oxidant stress.[159] The term "*oxidant stress*" is acknowledged to be vague. Moreover, as is the case with uremic solute retention, the changes that are easiest to measure may not be the most important contributors to illness. A variety

of evidence points to increased oxidant effects in uremia. Increased levels of primary oxidants cannot be documented because they are evanescent species that act locally like superoxide anion, hydrogen peroxide, hydroxyl radical, and hypochlorous acid. The accumulation of various products of oxidant reactions is therefore taken as evidence of increased oxidant activity. Although the accumulation of these markers of oxidant activity is well-documented, there is at present no explanation why the production of oxidants should be increased in uremia, except that increased quantities of hypochlorous acid may be released by phagocytes when uremia is accompanied by systemic inflammation.

Among the most commonly measured markers of oxidant activity are malondialdehyde and the other incompletely characterized substances that react similarly with thiobarbituric acid, but the accumulation of these low molecular weight compounds could reflect reduced renal clearance and increased production. More convincing evidence of oxidant stress is the accumulation of proteins containing oxidized amino acids.[160,161] The accumulation of these larger markers of oxidation cannot be attributed to reduced renal clearance. Further potential evidence of oxidative stress in uremia is the loss of extracellular reducing substances. The extracellular compartment is normally provided with several reducing substances, of which the reduced forms of ascorbic acid and plasma albumin are considered to be the most important. Presumably, oxidation of these "*sacrificial reductants*" limits damage to more valuable molecules when oxidants enter the extracellular fluid. In uremia, the portion of ascorbic acid and albumin circulating in the oxidized form is increased. The case of albumin, which undergoes oxidation at its single free cysteine thiol (SH) group, is particularly interesting. Plasma albumin in uremic patients is rapidly restored to the reduced form during hemodialysis.[162] The shift to oxidized albumin in untreated uremia is associated with the accumulation of cystine, which is the oxidized form of the thiol amino acid cysteine, and the shift back to reduced albumin during hemodialysis is associated with a lowering of cystine levels toward normal. One explanation for this phenomenon is that increased oxidant production causes increased oxidation of albumin and cysteine in uremia. An alternate explanation is that normal renal function is required to accomplish the steady reduction of cystine and albumin that must take place to offset normal oxidant production. Either way, loss of renal function would be associated with an increase in the ratio of oxidants to reductants in the extracellular compartment.

The major ill effect of increased oxidant activity in uremia is thought to be modification of proteins. Proteins are modified not only by direct oxidation of amino acids, but also by a combination of amino acid side chains with carbonyl (C=O) compounds. The terminology in this area is confusing. The first carbonyl compounds shown to react with proteins were sugars, and the modified proteins formed after several reaction steps were therefore referred to as AGEs. Elevated sugar concentrations could account for the increased AGE levels found in diabetic patients, but not for the subsequent findings of similarly increased AGE levels in uremic patients. Recent studies have shown that the high levels of active nonsugar carbonyls are responsible for the increased production of these modified proteins when renal function is reduced.[163] The active carbonyls have not been fully characterized, but they include compounds like glyoxal (see Figure 18-1) that can be produced by oxidation of both sugars and lipids. It has therefore been suggested that the protein end products of carbonyl modification in uremia should be referred to not as "*advanced glycation end products*" but as "*advanced glycoxidation and lipoxidation end products*."

Terminology aside, interest in both directly oxidized and carbonyl-modified proteins has centered on the possibility that alterations in protein structure contribute to uremic illness. Evidence has been gathered both for and against the important hypothesis that modifications of protein structure are responsible for accelerated atherosclerosis in uremic patients.[159,164,165] A contribution of modified proteins to dialysis related amyloidosis and skin pigmentation has also been identified.[164,166] It should be noted that modified protein structures are not thought to contribute to acutely reversible ill effects of uremia like confusion or nausea, but rather to cause gradual changes in tissue structure. The importance of such changes has likely increased as life with uremia has been extended by dialysis. The significance of protein carbamylation has also been extended beyond uremia. Cyanate, which is in equilibrium with urea, carbamylates lysine residues to form homocitrulline. Recently, protein carbamylation by cyanate has been demonstrated via myeloperoxidase-mediated oxidation of thiocyanate to cyanate at sites of inflammation and atherosclerotic plaque.[167] Furthermore, high plasma levels of protein-bound homocitrulline predicted cardiovascular events and death in a non-CKD population. This study demonstrates that the toxicity of "*uremic*" toxins may not be limited to those with CKD and ESRD.

Resting Energy Expenditure

Resting energy expenditure has been reported as increased, decreased, and normal in people with renal failure.[168–172] Choosing appropriate control populations and other methodological issues, such as the corrections for altered body composition, have probably contributed to this uncertainty. However, uremia apart from replacement therapies likely reduces resting energy expenditure. For example, energy expenditure falls with GFR in patients studied across a range of subnormal but not end-stage GFRs.[170,172] Also, in a study with careful attention to its control group and modern measurements of body composition by bioelectric impedance, a lower caloric use of 1325 kcal per day was noted in people with an average creatinine clearance of 29 ml/min compared to that of 1448 calories per day in the normal controls.[172] The lower energy expenditure also accords with rather consistent observations of lower body temperatures in uremia, although additional factors may be at play in thermoregulation.[7] The situation becomes more complex when patients on renal replacement therapy are considered. Indeed it is in this setting that some studies have reported higher that normal energy expenditure and that hemodialysis may further enhance metabolism.[171] Effects of inflammatory states in treated ESRD add yet another complexity to assessment of energy requirements.[173]

The lower metabolic rates in untreated uremia are likely to be of multifactorial origin. Lean body mass tends to be diminished with renal disease, and it is a major determinant

of energy expenditure.[172] However, diminished food intake may also influence basal metabolic rates and are often reduced.[174] Contributions of retention solutes have been suggested.[175] Finally, the normal kidneys themselves constitute an appreciable energy requirement given their high blood flow, filtration, and attendant transport work. Thus loss of this basal renal function has been suggested as another component of the fall in energy use with kidney failure.[170,176]

Carbohydrate Metabolism

Insulin resistance is the most conspicuous derangement in uremic carbohydrate metabolism.[177] The defect is clearly present in ESRD but in cross-sectional studies, impairment can be detected when GFR falls below 50 ml/min/1.73 m^2 with a graded relation to GFR.[178,179] The causes of this phenomenon are probably several. However, certain obvious possibilities do not seem to contribute. Insulin binding to its receptor operates normally in uremia and the receptor density is unchanged.[180,181] Also excess levels of glucagon or fatty acids do not account for the disorder.[177] Several hormones derived from fat, such as leptin, resistin, and adiponectin, accumulate with renal insufficiency. However, their correlations with measures of resistance are poor, and hence these accumulations seem to be insufficient as explanations.[177,182]

Because dialysis, transplantation, and low protein diets each improve insulin responsiveness, some authorities have suggested that a yet unidentified nitrogenous product mediates the insulin resistance.[177] In keeping with this possibility, an oral sorbent has improved the insulin response in uremic rats.[183] However, the exact factor(s) removed by therapies and presumably diminished in its production by low protein diets remains unknown. Acidosis is also relieved by dialysis, transplantation, and protein restriction. Because acidosis provokes insulin resistance and its treatment ameliorates the resistance, acid accumulation and nitrogenous wastes may contribute.[184] Finally, physical inactivity diminishes insulin action, and as patients become uremic, they tend to become deconditioned with probably a secondary contribution to insulin resistance. Indeed, exercise programs can mitigate the metabolic defect but must be relatively protracted with frequent training.[185,186] Thus uremic retention solutes including acid and simple inactivity likely constitute the major pathways to uremic insulin resistance.

Insulin resistance seems to have adverse effects. Most importantly it has been recognized as a risk for cardiovascular disease.[187] The connections between insulin resistance and vascular disease are not entirely clear. Of course a tendency to hyperglycemia is one toxic effect. Also some but not all investigators have suggested that renal salt retention stimulated by insulin may remain relatively sensitive with arterial hypertension as a result.[188,189] Insulin resistance is associated with coronary artery calcification and elevated plasma ADMA levels in CKD.[190] Another deleterious effect of insulin resistance outside of vascular disease might be loss of its anabolic action with consequent muscle wasting often seen with uremia.[177,191]

Even though insulin resistance is the rule in uremia, hypoglycemia can be a significant effect of renal insufficiency.[192] Hypoglycemia is likely to occur despite insulin resistance and for two main reasons. The kidney is a major site of insulin catabolism; thus insulin requiring diabetic patients may become hypoglycemic if their insulin doses are not adjusted as GFR declines. In effect, the higher levels of insulin in such patients overcome the resistance. In addition, the kidney is a major site of gluconeogenesis.[192] The liver produces the bulk of glucose in post absorptive and starvation states, but even in these situations, the kidney produces some glucose. With prolonged fasting, the kidney produces about half of the total glucose.[193,194] Thus severe renal disease may predispose to hypoglycemia by prolongation of the duration of insulin action and by reduction in gluconeogenesis, and these effects may be particularly apparent if other hypoglycemic factors such as ethanol ingestion or liver disease are at work.

Amino Acid Metabolism

Protein and amino acid metabolism can be deranged in uremia. Indeed, low serum albumin in ESRD patients is common and highly predictive of risk for death.[195] However, even absent nephrosis, hypoalbuminemia of some degree is common with renal insufficiency. In data from the MDRD study, 10%–15% of subjects with GFRs of 50–60 ml/min/m^2 had serum albumins below 3.8 mg/dl, and this proportion rose to almost 30% for those with GFRs at 10 ml/min/m^2.[149] This probably bespeaks generalized malnutrition often complicated by inflammation and/or acidosis but does not afflict all ESRD or pre-ESRD patients. Apart from these complications, isolated protein dysmetabolism is of at most modest effect in chronic kidney disease. Lim and Kopple in reviewing the topic concluded that "...uremia, per se, does not stimulate net protein catabolism."[191] Although dialysis may increase the dietary protein requirement somewhat through protein and amino acid losses into the dialysate (and perhaps because of some catabolic effect of the hemodialysis procedure itself), people with renal insufficiency but not on dialysis have no extra protein needs.[191] They can be maintained on low protein diets and stay in balance so long as acidosis or intercurrent inflammatory events do not occur. Although this picture seems accurate, such complications are common and raise the risk of marginal protein diets in the clinical setting.

The normal kidney participates in the metabolism of a number of amino acids. Loss of its function probably accounts for some of the alterations in plasma amino acid levels commonly described in renal insufficiency and ESRD.[2,196–198] For example, the kidney converts citrulline to arginine. Loss of this function likely contributes to the increasing citrulline to arginine ratio as GFR declines below 50 ml/min/1.73 m^2.[197,198] Similarly, the diminution of renal production of serine from glycine probably underlies the rise in the plasma glycine to serine ratio. Rising levels of the sulfur containing amino acid, cystine, taurine, and homocysteine are especially intriguing in light of their roles in redox balance, which is disturbed in uremia as noted previously, and the association of homocysteine with cardiovascular disease.[197–199] However, the mechanism(s) of these changes is unclear. These trends all appear as GFR drops below roughly one half of normal and gradually become more extreme as ESRD approaches. The pathophysiologic, import of these changes is largely uncertain.

Metabolic acidosis, of course, attends renal insufficiency and in its own right causes protein catabolism. Base supplements can mitigate these catabolic effects of acidosis.[184,200,201] Acidosis stimulates the ubiquitin-proteosome system of intracellular protein degradation via defects in the phosphatidylinositol 3-kinase/Akt pathway in muscle.[202] In addition to these effects of acidosis, it contributes to insulin resistance and thereby attenuates insulin's protein anabolic actions. Finally, activation of caspase-3 seems to be an important step in proteolysis followed by disposal of cleavage fragments through the proteosome.[203]

Lipid Metabolism

Nephrotic syndrome and probably even lower grade proteinuria is regularly associated with hyperlipidemia.[204] However, lipid abnormalities are of small proportion in renal insufficiency without major proteinuria. Indeed, total cholesterol falls as GFR drops below about 30 ml/min/1.73 m^2.[149] With respect to potentially hazardous changes, falls in HDL and rises in triglycerides have been described. LDL levels are usually not elevated and may be less than in normal controls.[204] The causes for these trends are unclear, although the decline in total cholesterol is taken to reflect, at least in part, progressive malnutrition. Even though the abnormalities are not quantitatively striking, the high rate of cardiovascular disease in the population with renal insufficiency has led to trials attempting to lower levels and reduce this risk. The largest trial in ESRD subjects with Type 2 diabetes found no beneficial effect of cholesterol lowering with a statin.[205] Whether the rate of decay in renal function can be influenced by lipid lowering is untested in a large trial. Potential effect in preserving renal function has been suggested by animal studies and small trials in humans.[204]

SIGNS AND SYMPTOMS OF UREMIA

The level of renal function at which uremia can be said to appear is obscure. There is no easily definable point in the fall of GFR when uremia supervenes. Furthermore, declines in several renal functions, not only glomerular filtration, are likely to confer symptoms and signs of uremia. In general, other functions such as ammoniagenesis, erythropoietin and 1, 25 hydroxy vitamin D syntheses, concentrating capacity, and tubular secretion are thought to track roughly with GFR. Nevertheless, defining the level of renal function solely by GFR may be at least in part misleading. For example, certain potentially toxic retained solutes appear to depend more on tubular secretion than GFR for their excretion, and the synthetic processes are probably linked to GFR only by virtue of general loss of functioning renal tissue. However, until particular renal dysfunctions are attached to specific aspects of the uremic syndrome, GFR will remain the principal index of renal function.

Most of the characteristics of uremia, both clinical and biochemical, have been defined in ESRD or at a level of GFR very near ESRD. Thus, as noted at the beginning of this chapter, in contemporary practice, uremic characteristics may be hard to dissect from complications of the dialysis procedure. Other comorbidities that are in principle separate from the uremia also commonly coexist with it. For example, the cardiovascular disease suffered especially by diabetic and hypertensive ESRD patients may be accelerated in some fashion by renal disease, but their myocardial infarctions, strokes, and peripheral vascular disease would traditionally not be considered pieces of the uremic syndrome. These conditions nevertheless add to the disability of the typical patient and often in ways that are not easily distinguishable from uremia or the "*residual syndrome*" of ESRD. Similarly, peripheral neuropathy and gastroparesis of diabetes are difficult to disentangle from uremic neuropathy and uremic anorexia, nausea, and vomiting.

Well-Being and Physical Function

Quality of life declines in people with chronic kidney disease. This is not so surprising given the well-known range of symptoms attributable to severe renal insufficiency (see Table 18-1). However, in recent years investigators have quantitated quality of life and efforts to relate it to level of renal function have begun to appear. Various questionnaires have been used to assess this complex attribute and worse scores compared to normal controls have been the consistent finding. The point in the course of renal disease at which quality of life begins to decline has not been dissected in great detail, but some data exist. In reviewing this area, the authors of the K/DOQI guidelines concluded that notable reductions in well-being appeared when GFR was less than 60 ml/min.[206] For example, subjects in the MDRD study with GFRs all less than 55 ml/min/1.73 m^2 were queried with several survey instruments and reported fatigue and reduced stamina that correlated with GFR.[207] In another study using the Medical Short Forms-36, people with GFR less than 50 ml/min/1.73 m^2 but not yet at ESRD scored lower than the general population in 8 of the 10 scales comprising the instrument.[208] Although these latter investigators could detect no gradient related to GFR within the group with depressed GFR, hemoglobin level did correlate with the scores.[208] Furthermore, patients with ESRD being treated with dialysis scored lower than those with renal insufficiency on all scales. By contrast, some studies using different questionnaires have found better quality of life in dialysis patients than in those predialysis.[206,209] However, transplantation and elevation of hemoglobin with erythropoietin have rather consistently been found to improve quality of life.[210,211] Thus patients with renal insufficiency and GFRs below 50 ml/min/1.73 m^2 generally have measurably diminished quality of life.

Physical functioning in patients treated with dialysis is decidedly below normal. The exercise capacity of these ESRD patients has been found to be about 50% of predicted with a range of 40 to 80%.[212] Treatment of anemia improves this situation but does not normalize it.[212,213] The most detailed studies have found a set of defects that are associated with easy fatigue.[214] These include both reduced muscle energetic failure and neural defects. The degree to which these lesions were attributable to the uremic environment itself, deconditioning of the patients, and the effects of their comorbidities has not been completely analyzed. Even selected highly functional dialysis patients display notable physical limitations. Blake and O'Meara have reported that among middle-aged dialysis patients with good

nutrition and no significant comorbidities, a wide range of quantifiable deficiencies exist.[215] For example, balance, walking speed and sensory function were all clearly below those of matched controls.

Although a definite diminution in function is prevalent in ESRD patients, the stage of renal disease at which defects appear has not been thoroughly assessed. One study of nondiabetic men less than 60 years old with GFRs less than 30 ml/min but not yet requiring dialysis found an exercise capacity that was relatively well-maintained at 94% of the reference value.[216] On the other hand, the same investigators using different measures found a clear reduction in strength in subjects older than 60 years with GFRs less than 25 ml/min.[217] Data from the National Health and Nutrition Survey III show a gradual increase in the fraction of subjects who thought they could walk one quarter mile from about 5% at normal GFR to 15% at a GFR of 15 ml/min/1.73 m^2.[206] Thus it is difficult to ascertain at what point in the course of progressive renal disease measurable declines in strength and exercise capacity appear, in part because different measures including the subjects' own estimates have been employed. However, functional impairment surely occurs before ESRD but may be hard to discern unless GFR is below 60 ml/min/1.73 m^2.

Neurological Function

Sensorimotor neuropathy was an early recognized component of the uremic syndrome.[7] However, it was usually assessed by measuring nerve conduction velocity and studied only at ESRD or very low GFR. Using conduction velocity and other tests the majority of ESRD patients have neuropathy, albeit often subclinical.[218,219] Hence, reductions in conduction velocity clearly occur at these late stages, but whether they begin to fall at higher levels of GFR is not certain. As with other uremic disturbances, the cause is unknown. Parathyroid hormone, multiple retention solutes, and more recently potassium have been associated with peripheral neuropathy but without definitive proof of causality.[218,219] Cognitive function can be severely disturbed in untreated uremia and can manifest as frank coma or catatonia relieved by dialysis.[218] Modern ESRD patients seem to show more subtle cognitive defects.[220] This seems likely if only because several studies suggest that impairment can be detected when GFR drops below 60 ml/min/1.73 m^2, and worsens as GFR falls.[221–223] As with other functions the degree to which cognition is influenced by uremia as opposed to other comorbidities, especially cerebrovascular disease, is difficult to ascertain, but clinically recognized vascular disease and other comorbidities were considered in these analyses. Subclinical cerebrovascular disease appears, to be common in the population with renal insufficiency, and its role in poor cognition needs further definition.[220,224]

Appetite, Taste, and Smell

Energy intake including protein intake declines as GFR does.[149] As with most of the abnormalities outlined previously, these phenomena appear to become detectable when GFR falls below about one half normal. Decrements in resting metabolism and physical activity diminish energy requirements and may appropriately dictate lesser intake.[172] However, an independent and clearly pathological anorexia also supervenes as witnessed not only at end stage, but also by falling serum albumin levels with lesser renal insufficiency.[149] In the NHANES III data, albumin levels begin to decline with estimated GFRs in the range of 50–60 ml/min/1.73 m^2.[206] A large number of pathways have been proposed as contributing to uremic anorexia. Acidosis, various inflammatory cytokines such as tumor necrosis factors and interleukins, and the adipogenic hormone leptin have been suggested as anorexigenic factors.[225–227] In addition to those factors inhibiting appetite, erosion of taste and smell have been long recognized and have been found almost ubiquitous in the ESRD population.[228,229] As with most defects, transplantation reverses the blunted smell.[228] Odor threshold appears to decline gradually with creatinine clearance.[228] Taste acuity has been reported as lower in dialysis patients than in those with renal insufficiency.[230] The factors responsible for these defects are unknown. Impaired olfactory function was associated with poor nutritional status but not with levels of retained uremic solutes in a small hemodialysis cohort.[231]

Cellular Functions

The most general cellular abnormality reported has been the inhibition of sodium-potassium ATPase (Na-K ATPase). Decreased Na-K ATPase activity in red cells of uremic patients was reported in 1964.[232] In general, subsequent reports have confirmed the observation, noted the same effect in other cell types, and emphasized that the inhibition was attributable to some factor in uremic serum.[233] The evidence for a circulating inhibitor includes the findings that dialysis reduces the inhibitory activity and uremic plasma can acutely suppress the pump activity.[233] However, the factor or factors have remained elusive. A number of candidates have been considered. Most attention has focused on digitalis-like substances. Recently several such compounds have been found in excess in humans with ESRD. These include marinobufagenin and telocinobufagin that have structures related to digitalis. In one report the plasma levels of each of these substances was four- to five-fold higher in ESRD patients compared to normal controls.[234] This particular study had the advantage of detailed mass spectrometry and nuclear magnetic resonance identification of the compounds with their concentrations determined by high-performance liquid chromatography. Many other investigations in the field have relied on antibody-based assays whose specificity may be less dependable. However, even should the elevations in these factors be confirmed, several issues remain to be resolved.

The compounds, including other digitalis-like factors, have generally been sought as endogenous products. The two compounds noted previously may be made by other animals, and some others, but apparently not these two, are synthesized by plants (as, of course, is digitalis). The question of overproduction, the dominant theme of the investigations in the field as opposed to accumulation of ingested material because of loss of renal function, has not been settled or much addressed. One study of uremic rats reported

an increased plasma level and urinary excretion of marinobufagenin.[235] Because both the excretion rate and the plasma level were about double the control levels, the results suggest that overproduction may be solely responsible for the increased plasma level and that the lower renal function in these subtotally nephrectomized rats played very little role. Similar measurements of the excretion or production for other digitalis-like compounds in humans or even in animals are not available.

If overproduction (and the data are not extensive for it) is the major cause of the higher plasma concentration of the digitalis compounds, the organ producing them and the stimuli to their secretion become important questions. The hypothalamus and the adrenal cortex have been the most studied as sources.[236,237] Both sites have been incriminated as sources of digitalis-like substances. Most studies have focused on various forms of experimental hypertension, and the relative roles of these two loci in uremia have not been addressed. ACTH may be a stimulus presumably to the adrenal forms. In any case, mice lacking the cardiac glycoside binding site in their Na-K ATPase are also resistant to ACTH-induced hypertension.[238] Expansion of the extracellular fluid volume has also been proposed as a stimulus.[239] How and where this signal is transduced is obscure. This view would hold that the substance has the effects of increasing cardiac output by cardiotonic digitalis-like actions and causing vasoconstriction through an effect on calcium entry in smooth muscle. These actions are proposed as promoters of hypertension, at least when sodium excretion is limited by renal disease.

Several considerations militate against digitalis-like substances as mediators of uremic toxicity. Some of the classical features of digitalis toxicity such as AV nodal conduction delays, ventricular extra systole, and visual disturbances are not prominent, even in older descriptions of untreated uremia. Other toxicities of digitalis such as anorexia are of course common with uremia.

The relation of Na-K ATPase inhibition to GFR has not been much explored. Most studies have employed sera from patients or animals with complete renal failure although some, such as a study of marinobufagenin in rats, have used models of renal insufficiency.[235] Also a report examining the depression in muscle membrane potential in humans with ESRD showed not only that the electrophysiological abnormality was improved by dialysis, but also that it was detectable at a GFR below about 10 ml/min/1.73 m^2 only.[240] This depression in muscle membrane voltage would be consistent with Na-K ATPase inhibition, and if so it seems a late event in the course of renal disease.

Why Is the Glomerular Filtration Rate So Large?

The disturbances discussed previously are generally undetectable unless GFR is less than one half normal. Thus one could argue that one half of renal function is superfluous. Because normal renal blood flow accounts for about one fifth of cardiac output, it would seem that a substantial fraction of cardiac output (and energy expenditure) serves no apparent homeostatic purpose. Homer Smith recognized that GFR was large in proportion to identifiable, important solute clearances and proposed that it was an evolutionary residual of the need to excrete water acquired as early vertebrates moved into fresh water from the sea. If so, the seeming superfluity of GFR would appear an expensive vestige in land dwelling mammals. Supporting structures such as bone have evolved with some safety factor, meaning that they can withstand some multiple of their usual load. Attractive as such an explanation may be for such a safety factor as the explanation for a greater than essential GFR, it begs the question of what that additional load might be. Although no clear conclusion can at present be drawn from these considerations, several suggestions can be offered for the apparent excess of normal GFR.

Fitness in an evolutionary sense may require the concentrations in body water of some excreted solutes to be maintained below the levels at which we detect disease. That is, our clinical criteria for uremic illness may be too coarse to detect the consequences of mild impairment of renal function. One might speculate that disturbances in an important but sensitive parameter, perhaps fertility, growth in children, or peak physical performance, would occur with less than doubling of some retained toxin. However, the sensitive function and the solute(s) that would depress it are unknown. In the same vein, perhaps in the past various toxins have appeared frequently enough in ingested food and/or were harmful enough that a rather high, constant clearance rate has been worth the metabolic cost. Again, the toxin is unknown. The apparent abundance in GFR has also been attributed to sporadic loads of dietary protein or phosphate. The known wastes of protein intake, urea and acid for the most part, do not seem to require the rates of clearance that usual renal function provides. Theoretically, the large tubular flow rate provided by the GFR could supply a sink into which organic solutes are secreted more favorably than at lower tubular flows. This hypothesis accounts for evolutionary development of a large GFR, but leaves unanswered the question of which solutes must be handled by secretion and thereby maintained at a low level in the extracellular fluid.

A full list of references are available at www.expertconsult.com.

Chapter 19

TIMING AND INITIATION AND MODALITY OPTIONS FOR RENAL REPLACEMENT THERAPY

Bessie Ann Young, M.D., M.P.H.

THE GROWING EPIDEMIC OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a growing worldwide epidemic that is estimated to affect over 26 million adult Americans,[1] which does not include the over 545,000 people who have kidney failure and currently require kidney replacement therapy (KRT) defined as dialysis or transplantation. The incidence and prevalence of kidney failure, administratively referred to as "end-stage renal disease" (ESRD),[2] are predicted to continue to increase and will affect an estimated 750,000 people by the year 2020.[3] The most recent United States Renal Data System (USRDS) reports indicate that the incident dialysis population has grown older, has more comorbid conditions than previous years, and is starting dialysis with higher levels of residual kidney function (RKF).[2] The incidence rate of new ESRD patients has increased to 360/million cases for U.S. adults, and African Americans now have the highest incidence rate of ESRD in the world (1010/million), followed by Native Americans (489/million), Asians (388/million), and whites (279/million). Furthermore, ESRD care is costly and accounted for 6.4% of the 2006 Medicare annual budget ($23 billion).[3] Therefore, timely and adequate preparation for KRT is essential to improve patient acceptance of KRT, avoid poor dialysis outcomes, improve overall survival and quality of life, and facilitate timely preparation for and receipt of kidney transplantation. This chapter will review important aspects of timing and selection of dialysis modalities and transplantation for KRT.

CHRONIC KIDNEY DISEASE CLINICAL GUIDELINES

In an effort to standardize the approach to and preparation for the initiation of dialysis, guidelines were proposed and published by the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) committee.[4] The NKF Advisory Board also approved the development of clinical practice guidelines to define CKD based on a classification system of subsequent progression. This allowed for development of a common language among those with and providers caring for patients with kidney disease.[5] CKD, defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for ≥ 3 months, is divided into five stages based upon GFR measures and other markers of kidney disease (blood, urine, or imaging studies) (Table 19-1). Evidence-based review of the literature and expert consensus established that the initiation of dialysis should occur when the GFR approached 10 ml/min/1.73 m^2.[5] For most patients who initiated dialysis in 2003, the mean estimated GFR was 9.8 ml/min/1.73 m^2. However, in 2006, USRDS data showed that almost 50% of patients started dialysis with an estimated GFR greater than 10 ml/min/1.73 m^2 and that mean serum creatinine fell from 8.7 mg/dl in 1995 to

TABLE 19-1 Stage of Chronic Kidney Disease

STAGE	DESCRIPTION	GFR (ml/min/1.73 m²)	ACTION
0	Normal kidney function with CKD risk factors	≥90 with CKD risk factors	Screening and CKD risk factor reduction
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment; reduction of cardiovascular risk factors
2	Kidney damage with a mildly decreased GFR	60-89	Estimate progression; continue risk factor reduction
3	Moderate decrease in GFR	30-59	Evaluating and treating complications
4	Severe decrease in GFR	15-29	Preparation for KRT
5	Kidney failure	≤15	KRT if uremic

6.4 mg/dl in 2007.[2] Some postulate that initiation of dialysis at higher levels of GFR may not be beneficial for patients and could be associated with greater dialysis associated morbidity and mortality compared to those who initiate dialysis at lower levels of GFR.[6] The most recent K/DOQI Guidelines recommend that initiation of KRT be based on the estimated GFR (using an appropriate estimating formula) or by measurement of the actual creatinine or urea clearance but not solely by measurement of the serum creatinine.[7] These guidelines are based on the assumption that estimated GFR adequately reflects overall kidney function and that uremic symptoms usually manifest at a GFR less than 15 ml/min/1.73 m². Ultimately, the decision to initiate dialysis or perform a preemptive transplantation is a joint decision between the patient and the physician, which should be guided by clinical indication.

UREMIC SYNDROME

Initiation of dialysis should be considered not only by stage of CKD, but also by uremic symptoms or when it is clinically indicated to start dialysis.[7] The uremic syndrome is a constellation of clinical and metabolic characteristics associated with fluid, electrolyte, hormonal, and metabolic abnormalities that develop as kidney function deteriorates. Piorry first used the term "uremia" (Latin for urine in blood) to describe the clinical condition associated with kidney failure.[8] Abnormalities associated with uremia include anemia, acidosis, elevated parathyroid hormone (PTH) levels, hyperphosphatemia, and an increase in middle molecules, such as beta-2 microglobulin, advanced glycation products, advanced oxidation protein, atrial natriuretic peptide, and others; however, no single toxin has been shown to be completely responsible for uremic symptoms. The uremic syndrome was thought to be present in late stage 4 or stage 5 CKD only. However, recent data show that uremic symptoms may be present at earlier stages of CKD and may contribute to the early incidence of cardiovascular disease in CKD patients.[9,10] Clinical manifestations of uremia include uremic frost, melanosis, uremic pericarditis, pulmonary edema, occult gastrointestinal bleeding, uremic fetor, nail atrophy, calcium-phosphate deposition, and signs of uremic encephalopathy or neurologic abnormalities (wrist drop, restless legs, headache, seizures, stupor, or coma).[8]

PREDIALYSIS CHRONIC KIDNEY DISEASE EDUCATION OPTIONS

According to the K/DOQI guidelines, patients should be referred by a primary care provider to nephrologists when they reach stage 3 CKD. Predialysis education should be initiated when patients reach stage 4 CKD (estimated GFR between 30 and 59 ml/min/1.73 m²). Stage 3 CKD evaluation allows for the assessment of CKD diagnosis, risk factor reduction (blood pressure and glucose control, and initiation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers), and complication (anemia and bone disease) treatment by a nephrologist, whereas education referral at stage 4 CKD allows adequate time for patient acceptance of CKD, preparation for hemodialysis access placement, and evaluation for preemptive transplantation or for cadaveric transplantation listing. Predialysis education should include information regarding the benefits of transplantation (living and donor and cadaveric); home dialysis therapies, such as peritoneal dialysis (PD), daily and thrice weekly hemodialysis, and nocturnal dialysis; and conventional in-center dialysis. Currently available predialysis education materials include those provided by NKF, American Kidney Fund, and others (Table 19-2). Fistula placement should be considered at this stage so that adequate time for fistula maturation can occur.[7] Finally, multidisciplinary CKD clinics have been shown to be an excellent method to facilitate diagnosis, education, transplant workup, and dialysis initiation in patients while still under the care of their primary provider.[11] CKD clinics have been shown to decrease first-year hospitalizations; improve survival; improve calcium, albumin, and access development;[12,13] and appear to be more cost-effective than traditional methods of CKD evaluation and referral.[12–17]

INDICATIONS FOR THE INITIATION OF DIALYSIS

Indications for initiation of dialysis include those associated with the uremic syndrome as stated previously (uremic pericarditis, muscle wasting, uremic encephalopathy, uremic neuropathy, malnutrition, weight loss, bleeding diathesis, or uremia associated nausea and vomiting) and other classic acute indications for dialysis initiation, such as severe metabolic acidosis, electrolyte abnormalities such as severe hyperkalemia associated with electrocardiogram changes and

TABLE 19-2 Calculation of Weekly K_rt/V_{urea}

STEP IN CALCULATION	EXAMPLE OF CALCULATION OR FORMULA
Calculate the urea clearance for a 24-hour period	Urea Clearance = U_{BUN}/P_{BUN} × urine volume ml/24 hr/1440 min = BUN ml/min
Determine the liters of urea clearance per week, which is equivalent to Kt	L/wk = Kt = BUN ml/min × number of minutes in week (10,080)/1000 ml/1 L
Determine the volume of distribution (V) of urea in liters (L)	$V(L)_{men}$ = 2.5 + 0.34* wt(kg) + 0.118*ht (cm) − 0.095*age (years) $V(L)_{women}$ = −35.3 + 0.18*W + 0.34*H or $V(L)_{men}$ = 0.6 × (wt in kg) for men $V(L)_{women}$ = 0.5 × (wt in kg) for women
Calculate the weekly Kt/V (Kt/V_{wk})	Kt/V_{wk} = BUN ml/min × number of minutes in week (10,080)/1000 ml/1 L V(L)
Example: 70-kg man with 24-hour urea clearance of 10 ml/min	**U_{BUN}/P_{BUN} × urine volume ml/24 hr/1440 min = BUN ml/min = 10 ml/min** **10 ml/min × 10,080 min/wk × 1 L/1000 ml = 100.8 L/wk BUN clearance** **Assess total body water (V) (approx. 0.6*wt)** **V(L) = 2.5 + 0.34*wt(kg) + 0.118*ht (cm) − 0.0958*age (years) (for men)** **V = 42 L** **Kt/V_{wk} = 100.8/42 = 2.4** **Conclusion: Kt/V_{wk} >2-pt does not yet need to start dialysis.**

severe fluid overload in the setting of decreased renal function, not responsive to diuretic therapy. Additional less tangible indications for initiation of dialysis include decreased cognitive ability, loss of appetite associated with decreased albumin, "failure to thrive", or frequent admissions or emergency department visits for uncontrolled hypertension or pulmonary edema associated with worsening kidney function.[6]

Calculation of Weekly KT/V

Although not discussed in the 2006 K/DOQI clinical guidelines,[18] the weekly renal urea clearance calculated as KT/V (K_rt/V_{urea}) was the primary criterion used to determine when to initiate dialysis in the 2000 K/DOQI guideline recommendations. Based on opinion, an actual weekly urea clearance less than 2 approximates an estimated GFR of 10.5 ml/min/1.73 m^2 when normalized to total body water. Calculation of the weekly Kt/V can give an objective functional measurement to aide in deciding when to initiate dialysis that is based on urea clearance rather than estimated GFR, which is creatinine-based. The weekly Kt/V is calculated using the 24 hour urea clearance, which is then extrapolated to the weekly urea clearance. The volume of distribution of urea is calculated based on standard formulas or based on weight and/or the total body water estimate. A weekly K_rt/V_{urea} equal to 2 is approximately equal to urea clearance of 7 ml/min and creatinine clearance between 9 and 14 ml/min/1.73 m^2.[19] An example of calculation of weekly Kt/V in a nondialysis individual is shown in Table 19-3.

Current K/DOQI Recommendations for Initiation of Dialysis

The current K/DOQI guidelines for initiation of dialysis transformed dialysis initiation into a stage-based paradigm, which uses either a calculated estimate of GFR such as the Modification of Diet in Renal Disease (MDRD) or an actual measurement of GFR.[4,20] These guidelines specifically state that dialysis-related education should begin at stage 4 CKD, and

TABLE 19-3 K/DOQI Recommendations for Initiation of Dialysis

CKD STAGE	RECOMMENDATION
Stages 1 and 2	Diagnosis of CKD and initiation of risk factor reduction
Stage 3	Referral from PCP to nephrologist for evaluation of CKD and assess risk factors for progression
Stage 4	CKD education, including education regarding transplant and dialysis Refer to vascular surgery for AV fistula once estimated GFR <20 ml/min/m^2
Stage 5	Preemptive transplant Cadaveric transplant wait-listing PD catheter placement for PD AV graft placement Initiate hemodialysis if uremic symptoms

referral for dialysis should be considered after the GFR decreases to 15 ml/min/1.73 m^2 (see Table 19-3).[2,7] Based on these guidelines, it was shown that initiation of dialysis in 2006 occurred at a higher mean GFR compared to 1994, at significant cost and possibly early loss of RKF.[2] Results from the Initiating Dialysis Early and Late (IDEAL) randomized trial, indicated that there was no demonstrable difference in mortality comparing early dialysis starts (eGFR 10-14) compared to late dialysis starts (eGFR 5-7) (see additional reference).[21] Current formulas for calculation of the estimated GFR are listed in the CKD K/DOQI Guidelines,[22] and most laboratories now include a calculated GFR based on serum creatinine based on the 4-variable estimated GFR equation proposed by Levey and colleagues (Table 19-4).[23]

Timeliness of Referral to a Nephrologist

Current referral patterns indicate that patients are not being referred to nephrologists in a timely fashion.[11] A National Institutes of Health (NIH) Consensus Conference Statement in 1994 defined timely referral to a nephrology provider as that occurring at least 4 months before the

TABLE 19-4 CKD-EPI Equation for Estimating GFR

RACE	SEX	SERUM CREATININE LEVEL, μmol/L(mg/dL)	EQUATION
Black	Female	≤62 μmol/L (≤0.7 mg/dL)	$GFR = 166 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
	Female	>62 μmol/L (>0.7 mg/dL)	$GFR = 166 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤80 μmol/L (≤0.9 mg/dL)	$GFR = 163 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
	Male	>80 μmol/L (>0.9 mg/dL)	$GFR = 163 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤62 μmol/L (≤0.7 mg/dL)	$GFR = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
	Female	>62 μmol/L (>0.7 mg/dL)	$GFR = 144 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
	Male	≤80 μmol/L (≤0.9 mg/dL)	$GFR = 141 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
	Male	>80 μmol/L (>0.9 mg/dL)	$GFR = 141 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$

CKD, chronic kidney disease; *GFR*, glomerular filtration rate; S_{cr}, serum creatinine.
A.S. Levey, L.A. Stevens, C.H. Schmid, et al, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.

initiation of dialysis,[27] whereas the Canadian Society of Nephrology referred to timely referral as that occurring at least 12 months before the initiation of dialysis.[28] It is currently estimated that 20%–80% of patient are categorized as late referrals to nephrologists (4 to 6 months before the initiation of dialysis) depending on the population evaluated.[11] Late referral to dialysis has been associated with a 37% (HR=1.37, 95% Confidence Interval [CI] = 1.22–1.52, $p<0.001$) greater mortality than early referral at one year postinitiation of dialysis and is associated with greater morbidity as well.[29] Predialysis nephrology care (defined as referral to a nephrologist 3 months or more before the initiation of KRT) is associated with 41% greater wait-listing for transplant and 54% greater chance of receiving a kidney transplant.[30] Even after adjusting for access to care before the initiation of dialysis using propensity score analysis, later predialysis nephrology referral is associated with worse mortality compared to early referral.[31] Furthermore, early predialysis care has been associated with improvement in anemia,[32] cardiovascular disease, access placement, and quality of life.[13,16,33,34] Early predialysis nephrology care should be the ultimate goal for all patients with stage 3 and greater CKD.

Factors Associated with Late Nephrology Referral

Later referral of CKD patients to nephrologist is a worldwide phenomenon, and affects from 20%–80% of CKD patients.[11,35] Factors associated with late nephrology referral include those associated with both patient and healthcare system characteristics.[36,37] A systemic review of factors associated with late nephrology referral showed that older age, existence of multiple comorbidities, racial and ethnic minorities, lower educational level, and lower socioeconomic status were significant patient factors associated with late referral in CKD, and lack of insurance and type of referral center were healthcare system-related factors.[36] Additional practitioner-related factors include lack of knowledge regarding appropriate timing for dialysis referral, lack of communication between referring primary care providers and nephrologists, and inadequate training in CKD referral guidelines.[38,39] Late referral was also associated with care by a general interest compared to primary care received from a family practitioner or other primary care provider.[39] Improved education of and interaction of nephrologists with primary care providers may help to improve outcomes in dialysis patients and are necessary to change the trends in late CKD referral.[36]

DIALYSIS MODALITY SELECTION

Dialysis modality selection is one of the most important decisions a patient must make regarding KRT, but one that we often expect patients to make during a relatively short period of time, such as during a clinic visit. Many educational programs are available as videos or DVDs or as internet programs that can assist patients and their families to decide which modality fits best with their lifestyle and needs (Table 19-5). In addition, patients should also have the

TABLE 19-5 Kidney Replacement Therapy Educational Resources

PROGRAM/MATERIALS	WEBSITE
National Kidney Disease Educational Program	www.nkdep.nih.gov/resources/index.htm
National Kidney Foundation	www.kidney.org
Fistula First Breakthrough Initiative	www.esrdnet11.org/assets/coalition/pcp_educational_resources.pdf
American Association of Kidney Patients	www.aakp.org
Centers for Medicare & Medicaid Services (CMS)	www.cms.hhs.gov/MedlearnProducts
National Kidney and Urologic Diseases Information Clearinghouse	www.kidney.niddk.nih.gov
Renal Physicians Association	www.renalmd.org
Hypertension, Dialysis and Clinical Nephrology	www.hdcn.com
United States Renal Data System	www.usrds.org
American Nephrology Nurses Association	www.annanurse.org/cgi-bin/WebObjects/ANNANurse
Medical Education Institute	www.kidneyschool.org www.lifeoptions.org
Home Dialysis Central	www.homedialysis.org
Northwest Renal Network	www.nwrenalnetwork.org

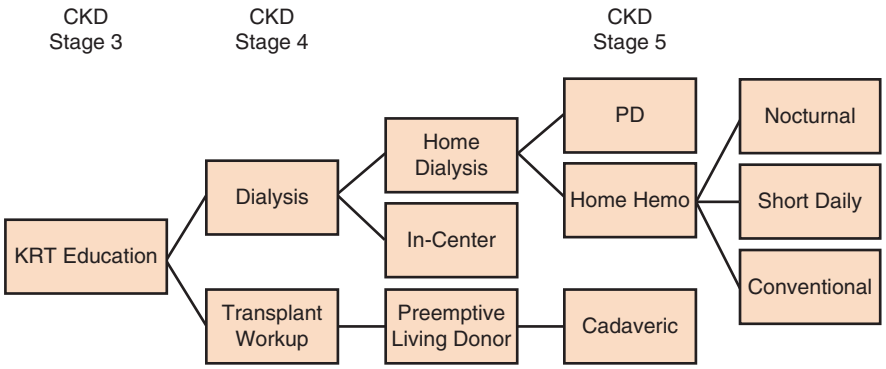


FIGURE 19-1 Paradigm shift in initiation of renal replacement therapy. Stage 3 CKD patients would receive education regarding all types of KRT but would be worked up for a living donor kidney or get wait-listed for a cadaveric kidney. If a kidney were not available, patients would first initiate home dialysis modalities and transfer in-center if they failed at home.

opportunity to discuss modality selection with a patient peer who is on dialysis or has a transplant, and a trained dialysis social worker who is familiar with all aspects of KRT (transplant, conventional, home dialysis including hemodialysis and peritoneal), to gain sufficient exposure to the various KRT modalities available. Furthermore, U.S. patients should also have access to a financial specialist who can assess current health insurance dialysis coverage, and help patients decide whether addition insurance coverage is needed for adequate dialysis treatment coverage. Although the U.S. ESRD entitlement program pays for the majority of dialysis-related healthcare, it may not cover all care, which may be state dependent. Evaluation of patients for preemptive transplant before the initiating of dialysis should be considered for all patients, as should listing for transplant as soon as possible, or simultaneously as patients are being prepared for dialysis (Figure 19-1).

Kidney Replacement Therapy Timing

As stated previously, recommendations for initiation of dialysis are now CKD stage-based. Many more patients are initiating dialysis at estimated GFR levels of 15 ml/min/1.73 m^2. Patients should be considered for preemptive transplant once they reach stage 4 CKD (estimated GFR <30 ml/min/m^2) and/or at the discretion of the local transplant centers' and/or organ sharing networks' recommendations. Currently, some ESRD networks require that patients initiate dialysis before being considered for a transplant or kidney transplant wait-listing, which forces these patients to initiate dialysis to have insurance that will cover transplantation. Based on K/DOQI guidelines, we recommend dialysis be considered once the GFR reaches 15 ml/min/m^2 and patients have other indications for initiation of dialysis. Initiation should be based on clinical symptoms of uremia and the CKD stage.

DIALYSIS IN THE ELDERLY

Because elderly patients may not eligible for a kidney transplant, dialysis therapy remains the primary means of KRT. Recent data, however, suggest that the elderly (85 years and older) may not progress to ESRD as rapidly as the nonelderly. In a retrospective cohort study of veterans identified with stages 3–5 CKD, elderly patients were less likely to survive than younger patients with similar levels of estimated GFR. Elderly patients were also less likely to initiate dialysis before death.[40] Additionally, in veterans with stage 4 CKD, those 85 years and older were less likely to receive a dialysis access but also less likely to progress to ESRD. In theoretical scenarios, the elderly were less likely to survive late stage CKD before the initiation of dialysis and were more likely to be exposed to unnecessary procedures compared to younger patients.[41] Therefore,[18] a patient's clinical status, comorbid conditions, age, and frailty may dictate whether permanent dialysis access should be placed once the estimated GFR is less than 20–25 ml/min/1.73 m^2 and whether a patient wishes to consider initiation of dialysis.

DIALYSIS ACCESS

The most recent K/DOQI Guidelines recommend that all stage 5 CKD patients have a functioning dialysis access before the dialysis initiation and that hemodialysis access be in place at least 6 months before the initiation of dialysis.[7] Recommendations for PD access are that a catheter be placed at least 2–4 weeks before the initiation of PD.[18] The Society for Vascular Surgery clinical practice guidelines mirror those of K/DOQI, except for recommendations that patients be sent for vascular surgeon evaluation when they reach late stage 4 CKD (estimated GFR <20–25 ml/min/1.73 m^2) and that arteriovenous (AV) access be constructed as soon as possible to allow enough time for fistula maturation and to ensure that the access is ready for use at the time of initiation of dialysis.[42] K/DOQI guidelines recommend that prosthetic access be placed 3–6 weeks before the anticipated date of dialysis and patients with stage 5 CKD be educated on the risks and benefits associated with catheters, such that timely creation of a fistula be considered and accepted by the patient to avoid the need for a temporary catheter.[18]

Fistula First Breakthrough Initiative

Created as a means of quality improvement to encourage the use of autogenous (native) AV fistulas for the incident dialysis, the Fistula First Breakthrough Initiative (FFBI) was jointly developed and implemented by Centers for Medicare and Medicaid Services (CMS) and the ESRD networks to improved overall outcomes for vascular access in the United

States.[43] The initial goal was to increase the use of fistulas to 50% of incident patients and 40% of prevalent patients. This goal was subsequently increased to 66% of prevalent patients using fistulas by 2009. Data suggest that as a result of the FFBI, AV fistula use has increased while graft placement has decreased; however, chronic catheter use has increased as well. This has resulted in increased primary AV fistula failures, increased risk of catheter associated infections, and increased costs associated with the initiative.[44] Currently, K/DOQI guidelines recommend working AV fistulas should be the hemodialysis access of choice, followed by AV grafts, and lastly by chronic dialysis catheters, which should be avoided if possible.[18]

1. *Arteriovenous Fistula*. Besides the classic AV radiocephalic fistula described by Brescia and colleagues in 1966,[45] several variants on the classic autogenous fistula have been used for surgical AV fistula formation. Current recommendations from K/DOQI,[18] FFBI,[43] and the Society for Vascular Surgery[42] all recommend that patients who have chosen hemodialysis as their choice of dialysis modality undergo preoperative venous mapping or imaging so that adequate vessels can be used for AV fistula formation. Duplex Doppler ultrasound is the preferred method of vascular mapping, but other methods of imaging can also be used.[18,42] It is recommended that AV fistulas be created distally in the lower arm first to save the vessels, followed by graft placement or upper arm fistulas, so that if the lower access fails, the upper arm is still available for access placement.[18,42] Additional autogenous AV fistulas that can be created include the lower arm brachiocephalic, radial-, ulnar-, and brachial-basilic transposition fistulas, and upper arm brachiocephalic AV fistulas and transpositions (Figure 19-2).[42] Additional fistulas can be created in the lower extremities (femoral greater saphenous, femoral artery to femoral vein). Additionally, upper chest grafts can be considered if extremity AV fistulas are not an option.[42]
2. *Arteriovenous Graft*. Although AV grafts have been used for a large percentage of AV dialysis access in the past, the FFBI decreased the overall utilization of AV grafts in incident and prevalent dialysis patients.[43,44] AV grafts are associated with a 78% increased risk of access failure compared to autogenous fistulas[46] and are twice as likely to fail compared to autogenous fistulas when revised.[47] Although AV grafts have been classically associated with decreased longevity, greater overall costs, and greater infection risk than AV fistulas, some authors suggest that prior analyses failed to take into consideration fistula failure as a result of failure of AV fistula maturation.[48] However, it has also been shown that once placed and fully functioning, AV fistulas are associated with fewer procedures, infection, and costs compared to AV grafts.[46] More recent data suggest that AV grafts be considered as a bridge to AV fistula placement so that dialysis can be initiated without the use of a tunneled catheter.[42] Furthermore, newer surgical techniques include lower forearm placement of a dialysis graft, allowing for maturation of upper arm vessels, which can then be used for brachiocephalic fistula creation in the upper arm.[42,49]
3. *PD Catheter Placement*. PD is the treatment of choice for those who are initiating dialysis and have not contraindication for PD catheter placement. Placement of PD catheter should be considered 2–4 weeks before the need to start dialysis once a patient reaches stage 5 CKD (estimated GFR <15 ml/min/m^2).[18] Patients should be assessed by a physical exam before the PD catheter placement to confirm that no major contraindications exist before catheter placement. Absolute PD catheter contraindications recommended by K/DOQI include: inability to physically or mentally perform PD in the absence of a suitable assistant, and abdominal wall defects such as severe abdominal irreparable hernia, omphalocele, gastroschisis, diaphragmatic hernia, and bladder extrophy.[19] PD catheter

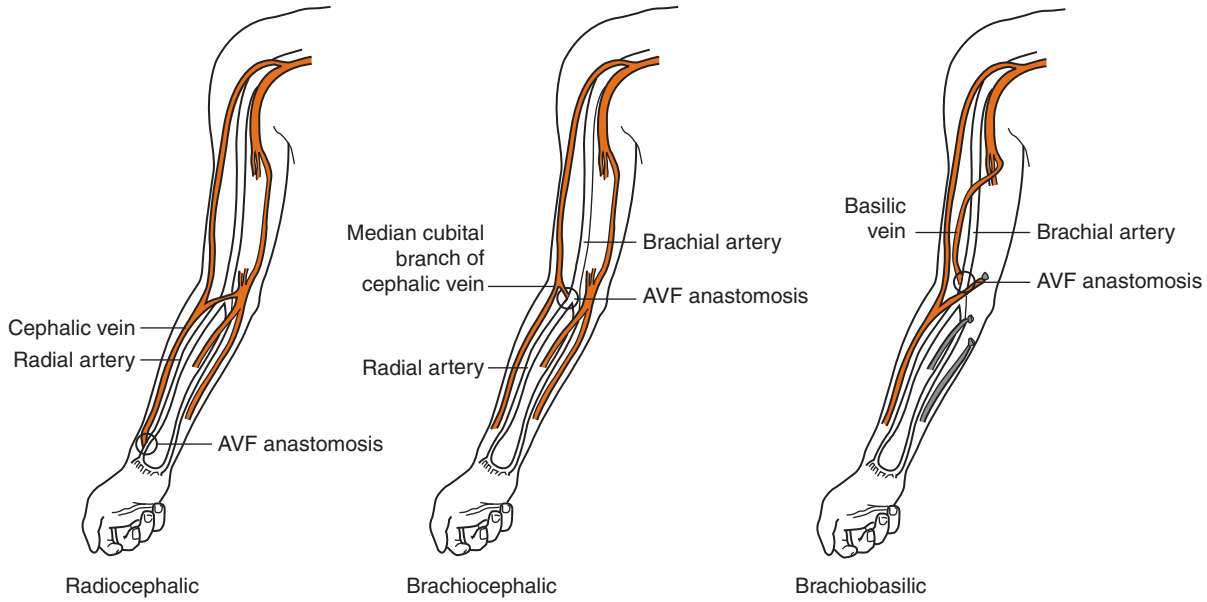


FIGURE 19-2 Types of autogenous fistulas. (Adapted with permission from M. Allon, M.L. Robbin, Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions, Kidney Int 62 (2002) 1109-1124.)

placement should be done by a nephrologist or surgeon experienced in catheter placement. There are several PD catheters to choose from; the one used most often and with the best outcomes still appears to be the Tenchkoff double cuffed catheter. Laparoscopic placement of PD catheters is now being done to facilitate direct visualization of catheter insertion.[50]

CHOICE OF DIALYSIS MODALITY

The choice of dialysis modality should be based on patient preference, clinical appropriateness, and physician recommendations.[18] Unless patients have an absolute contraindication, PD should be considered as one of the first forms of therapy as should home hemodialysis modalities. If patients are not immediate transplant candidates or not appropriate PD candidates, home hemodialysis (conventional, daily, or nocturnal) may provide similar survival compared to a cadaveric transplant (Figure 19-3).[51,52] Patient education regarding kidney replacement modality should be initiated as early as possible (stage 3 or 4), such that patients can make informed decisions regarding preference for dialysis modality if transplantation is not an immediate option.[18] Options for KRT are reviewed below.

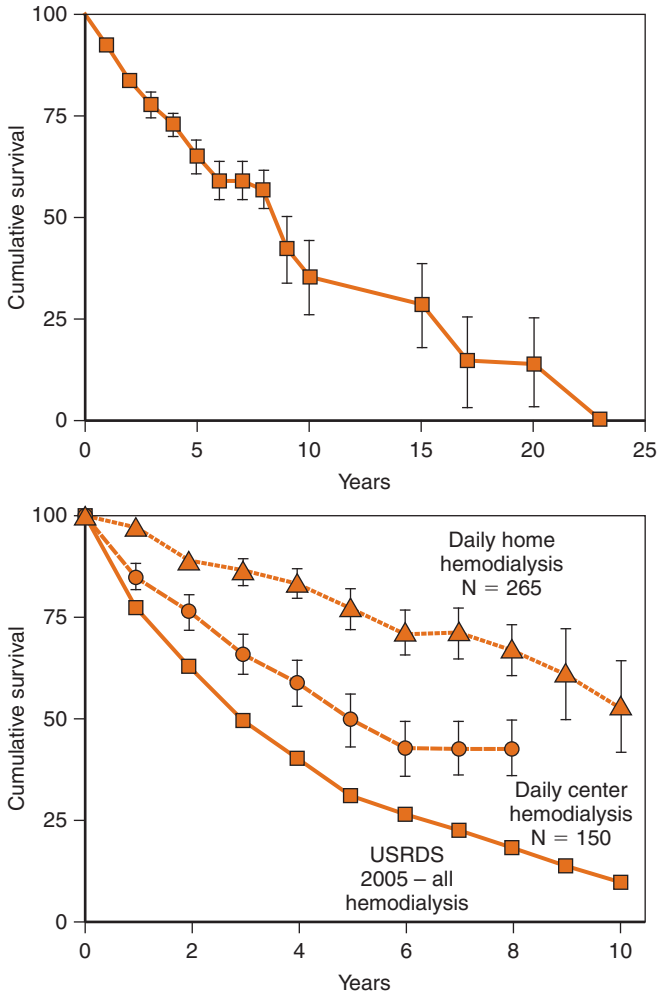


FIGURE 19-3 Survival 415 short daily hemodialysis patients *(upper panel)* compared to daily center hemodialysis and mortality in all United States Renal Data System (USRDS) hemodialysis patients *(lower panel)*. (Data from C.M. Kjellstrand, U. Buoncristiani, G. Ting, et al., Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years, Nephrol. Dial. Transplant. 23 (10) (2008) 3283-3289.)

HOME DIALYSIS MODALITIES

Peritoneal Dialysis

PD has been available since the development of the PD catheter perfected by Tenchkoff in the 1960s.[53,54] Further advances in PD bags and catheters have decreased the rates of peritonitis, which has allowed for more patients to choose this modality than ever before. PD involves the placement of a PD catheter within the abdomen such that PD fluid can be infused and toxins can be dialyzed out of the body, using the peritoneum as the dialysis membrane.[19] PD can be performed at home as chronic ambulatory peritoneal dialysis (CAPD) during which patients exchange 2–2.5 L bags of dialysate four times a day. This compares to chronic continuous peritoneal dialysis (CCPD), during which patients cycle at night and may leave their abdomen dry or wet during the day.[55] Comparing PD training to conventional center dialysis, incident patients on PD were more likely to be satisfied with their dialysis compared to hemodialysis and were 46% more likely to rate their dialysis experience as excellent compared to hemodialysis patients.[56] PD remains a viable dialysis modality that should be considered as one of the first line methods of KRT second to transplant and other forms of home dialysis.

Home Hemodialysis

Home hemodialysis provided 4.2% of KRT in 1980 compared to 89.3% center dialysis and 3.6% PD, but in 2006 provided only 0.7% of KRT, compared to 91.7% center and 7.4% PD.[2] With the advent of new home hemodialysis machines that allow patients to perform dialysis more easily and that do not require home modifications as compared to conventional machines,[57,58] home hemodialysis has undergone resurgence in the number of patients considering home modalities. In addition, home hemodialysis can be used to offer conventional thrice weekly hemodialysis, nocturnal dialysis, and in some cases, more frequent dialysis (4 or more days per week) using conventional dialysis machines. Although there has never been a randomized controlled trial that compares center dialysis to home hemodialysis, observational data suggest that home hemodialysis therapies are associated with better survival, quality of life and improvement in comorbid conditions compared to center hemodialysis.[52,59] The results of the NIH-sponsored Frequent Hemodialysis Network (FHN) randomized controlled trial[60] will allow comparison of home-based nocturnal therapies with daily center dialysis, but will not answer the question as to whether other home modalities (thrice weekly or short daily) are better than comparable center-based therapies.

1. *Conventional Home Hemodialysis*. Conventional dialysis can be done in the home using regular dialysis machines and a trained dialysis helper.[61–64] Several units across the country continue to support conventional home hemodialysis, which requires patient and helper in depth training (usually for 4–6 weeks), modifications to the

home (additional drain, electrical outlet, and backflow preventer) such that traditional reverse osmosis water systems can be used. In addition, 24 hours a day, 7 days a week nursing support of patients is also needed. Conventional home dialysis is associated with better quality of life and survival,[65,66] even after taking into account comorbid conditions. Home helper failure is associated with older age, but not comorbid conditions, ethnicity, or type of helper. Better home survival was associated with younger age and primary renal disease other than diabetes and a related home helper.[64] Fewer patients chose thrice weekly dialysis at home because of the newer machines available; however, conventional thrice weekly home hemodialysis remains a viable option for patients interested in a home dialysis therapy.

2. *Short Daily Hemodialysis*. Short daily dialysis has been offered in some units as a method of in-center dialysis, but it is difficult to sustain because of patient travel, preference, and staff overhead. Currently, short daily dialysis can be offered as a home hemodialysis method using conventional dialysis machines or specialized daily dialysis machines such as the NxStage System One. The NxStage allows patients to dialyze at home 2 or more hours 5–6 days per week.[67,68] Daily dialysis has been associated with better quality of life, improved depression, better anemia, and phosphate control compared to conventional dialysis in observational studies.[59] The NxStage System One machine is portable and can be stowed as cargo on airplane trips or in placed in trunks of cars or cruise ships. Other dialysis machines have yet to undergo Food and Drug Administration approval for home use. The ongoing FHN Trial, an ongoing randomized controlled trial between short daily in-center dialysis and nocturnal home hemodialysis, will help to determine the most adequate method of daily dialysis. Several observational studies suggest that patients who dialyze daily have similar survival outcomes compared to cadaveric transplant recipients. If a patient is not an acceptable transplant candidate or is likely to be on the waiting list for an extended period of time, more frequent dialysis should be considered as the primary mode of KRT.[61,69]
3. *Nocturnal Hemodialysis*. Nocturnal dialysis is a daily or every other day dialysis modality whereby dialysis patients dialyze at night for 6–8 hours or more using low dialysate flow and low blood flow rates. Usually patients need systemic anticoagulated with heparin or other methods during their treatment and should have a partner or dialysis helper assisting them at home. A randomized trial of nocturnal dialysis versus conventional thrice weekly dialysis showed that nocturnal dialysis was associated with improved phosphate, blood pressure, and kidney quality of life measures, and decreased left ventricular mass.[70] Nocturnal dialysis can also be performed in-center but requires a center with a designated staff and setup that will allow patients to sleep while on dialysis. In observational studies, home nocturnal dialysis has been shown to be 20% more cost-effective than conventional in-center dialysis. The FHN randomized controlled trial will help establish the best method of daily dialysis delivery for patients comparing in-center daily therapy to home nocturnal dialysis.[60]

IN-CENTER DIALYSIS

The majority of U.S. dialysis patients initiate dialysis with conventional center-based therapy three times a week for 4 hours each run.[2] Patients may initiate in-center dialysis starting with a short run (2–3 hours) with a low flux dialyzer, low dialysate, and blood flow, which is subsequently increased over a period of 2–3 days to standard blood flows (350–400 ml/min) and standard dialysate flows (500–800 ml/min). A typical conventional dialysis prescription is usually for 4 hours, three times per week, using a high flux dialyzer and high dialysate flows (500+ml/min). With adequate preparation time, patients can initiate dialysis in center and do not need to be admitted to the hospital for their initial dialysis run.[7]

Switching from Peritoneal Dialysis to Hemodialysis

Although PD is one of the simplest and most cost-effective dialysis modalities, most patients cannot remain on PD indefinitely. In addition, controversy exists as to outcomes compared to hemodialysis. PD has been associated with worse, similar, and better mortality compared to hemodialysis, depending on the study and statistical analysis. In a recent prospective national observational project, the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study, patient survival was not significantly different between PD and hemodialysis patients after the first year, but were twofold greater for PD patients compared to hemodialysis patients the second year of follow-up. Differences from years 1 to 2 were thought to be the result of loss of residual renal function and increased cardiovascular disease associated with PD.[71] In addition, 25% of PD patients and 5% of hemodialysis patients switched modality.[72] Predictors of switching from PD to hemodialysis included increased body mass index and black race, although there was no difference in overall mortality between switchers and nonswitchers. Thus PD is an excellent modality for initial dialysis therapy when it is known that a patient has a transplant that will occur within a short period of time, for those who want to be in more control of their dialysis, or for those who are motivated to do dialysis at home. Once residual renal function is sufficiently decreased, care must be taken to assure patients are adequately dialyzed, which can be accomplished with current methods of CCPD.[18,19] Unless there is a major contraindication, PD should be considered as first line therapy for all patients secondary to preemptive kidney transplant and other home dialysis therapies.

TRANSPLANTATION

Transplantation is the preferred method of KRT for all patients but is limited by the number of cadaveric kidneys available (18,000 in 2006) and by the lack of availability of living donors.[2] Growth of kidney transplants increased 3.5% in 2005, which was due, in part, to the use of expanded criteria cadaveric donors; however the number of patients wait-listed grew 8% in the same time period. Currently, over 70,000 patients are listed for transplant and over one third of

those (46,000) are active on the transplant waiting list. Transplantation is associated with the best survival for all patients regardless of race or underlying comorbid condition.[73] Transplantation can be accomplished by living donor (related or unrelated) or by cadaveric kidney. Patients must undergo a thorough cardiac and pulmonary workup such that a transplantation center feels that patient can undergo transplant surgery successfully. The various types of transplantation are briefly described below. The median time to cadaveric transplant is currently over 4 years, and if a patient is sensitized, the wait is 6 years. Over 16% of patients die waiting for a transplant, and 12% of white patients compared to 22% of nonwhite patients will wait more than 5 years for a transplant after being listed.[2]

1. *Living Donor*. Living donor transplantation affords the best KRT for most patients who are medically eligible to receive a kidney transplant.[2] In an attempt to increase the pool of live donors available, the transplant community has pursued multiple live-donor venues. Currently, living-related or living unrelated kidneys are potentially available from suitable donors. Using these methods of live kidney donation, the number of live donor kidney transplants have almost doubled over the last decade in the United States and Canada;[74] however, the rates of living-related donated kidneys has declined over the last few years, the rates of living distant or unrelated donors has increased significantly and now account for almost 45% of transplants.[2] Live donation kidneys have better 1 year kidney graft survival (95%) compared to deceased donor kidneys 90%).[2] Donors may be related, unrelated, or altruistic; or transplant may occur as part of a multiple donor swap, which is available at some transplant centers. Although payment for kidneys is illegal in the United States and most countries, thousands of kidneys are sold on the black market in other countries.[75,76] Debate as to the best methods to increase live kidney donation continues.
2. *Deceased Donor Kidney Transplant*. Although live donor transplantation has increased considerably in the US, cadaveric kidney transplant remains the primary mode of kidney transplantation. Deceased donor transplant accounted for 59% of kidney transplants performed in 2005, and approximately 76% of kidneys were from standard criteria donors, whereas 16% were from expanded criteria donors (ECD).[2] Cadaveric transplantation outcomes have improved considerably over the last 2 decades, primarily because of the rise in use of ECD kidneys. According to USRDS data, approximately 45% of incident and prevalent ESRD patients are willing to accept an ECD kidney.[2] ECD characteristics include age $\geq$60 years or 50–59 years with at least two of the following histories of hypertension, serum creatinine level >1.5 mg/dl (132.6 moles/L), and cerebrovascular cause of death.[77] In a retrospective cohort study, investigators found that ECD recipients were more likely to survive long-term (3 years) compared to those who remained on the wait list or received a non-ECD kidney but had greater early mortality. Those older (>40 years), nonwhite, and with diabetes benefited the most from ECD kidney transplant.[77]
3. *Preemptive Transplant*. Preemptive transplant does not have wide acceptance in the United States because of the limited number of kidneys available for transplantation, the discouragement of preemptive cadaveric transplant by certain ESRD networks, and the need for insurance coverage for the significant workup of living donors before transplantation. Preemptive transplantation accounted for 2,419 (2.22%) of the over 108,000 incident KRT patients in 2006 and has been associated with improved dialysis associated morbidity, quality of life, lower KRT costs, and higher posttransplant employment rate.[78] Preemptive kidney transplantation is also associated with 14% better transplant kidney survival compared to kidneys transplanted after initiation of hemodialysis. Preemptive transplant is also associated with 18% better recipient survival compared to hemodialysis, whereas PD before transplant was associated with 3% better survival ($P<0.001$) compared to hemodialysis.[79] In addition, patients who learned about transplantation from someone other than their nephrologists were 2.46 times (95% CI=1.24–4.88) less likely to receive a preemptive transplant compared to those who heard about transplantation from their nephrologist, which suggests that there are substantial missed opportunities for preemptive transplantation by nephrologist.[80] Therefore, preemptive transplantation is virtually limited to those with an available living donor and insurance coverage that will allow transplantation before the initiation of dialysis, and is associated with better transplant and recipient survival compared to hemodialysis.

SPECIAL CIRCUMSTANCES

Acute Kidney Injury

Acute kidney injury (AKI) has been associated with poor patient outcomes and has been shown to be a significant risk factor for chronic KRT. Although this review is focused on timing of chronic KRT in stage 5 CKD patients, many AKI patients require chronic KRT. Review of observational studies of critically ill patients shows that late timing of KRT was associated with lower mortality compared to early initiation of dialysis and was associated with a longer duration of KRT, number of days of hospitalization, and greater dialysis dependence compared to early initiation of KRT.[81] In addition, recent data from the Veterans Affairs/NIH Acute Renal Failure Trial Network showed that daily versus conventional intermittent hemodialysis did not decrease mortality or improve recovery of kidney function in critically ill patients with AKI.[82] Meta-analyses of available studies indicate that AKI is a risk factor for CKD, ESRD, and mortality, particularly in the elderly.[83,84]

CONCLUSIONS

Opinions regarding KRT timing have undergone significant changes over the last decade, due, in part, to the stage-based approach to initiation of KRT in stage 5 CKD patients. Preemptive transplantation is the preferred method of KRT, but, because of the increasing number of patients who have CKD and will need KRT, there are not enough available transplants and other methods of KRT will still be needed. PD and other home dialysis modalities such as short daily

and nocturnal dialysis are underutilized methods of KRT. In addition, some home hemodialysis modalities may approach the survival found with transplantation and should be considered as preferred methods of KRT when transplantation is not available. A paradigm shift of preparing patients for all modes of KRT, including transplantation, before the need for initiation of dialysis may improve overall survival and quality of life for ESRD patients. Home dialysis therapies such as PD should be considered as first choice for KRT, especially when patients have significant residual renal function or have an impending living donor transplant. Finally, newer home hemodialysis modalities such as daily or nocturnal dialysis may provide better survival for patients who are not immediate transplant candidates.

A full list of references are available at www.expertconsult.com.

Chapter 20

PRINCIPLES OF HEMODIALYSIS

Jane Y. Yeun, M.D., and Thomas A. Depner, M.D.

Hemodialysis is a life-sustaining treatment without which more than a million patients throughout the world would die, most within a few weeks.[1,2] This dependence on an extracorporeal blood device is both the fulfillment of hopes by some and the dashing of dreams by others and highlights the need for an in-depth understanding of all aspects of hemodialysis, including the human reactions to it. Before one can configure hemodialysis optimally, one must understand its target, the uremic syndrome. In this chapter we review the physical, chemical, and clinical principles of hemodialysis as they relate to the treatment of uremia, starting with historical milestones and ending with projections for the future. The discussions include brief notes of comparison to other modalities, such as peritoneal dialysis and hemofiltration, that are reviewed more extensively in other chapters.

FUNDAMENTAL CONCEPTS

Historical Development

Hemodialysis was originally termed *extracorporeal dialysis* because it was performed outside of the body.[3] Several early pioneers laid the foundation for therapeutic dialysis. Graham (1805-1869), a professor of chemistry in Scotland, invented the fundamental process of separating solutes using semipermeable membranes in vitro and coined the word "dialysis."[4] In 1916, Abel in the United States dialyzed rabbits and dogs with a "vividiffusion" device using celloidin membranes and a leech extract called hirudin as an anticoagulant.[5] Abel was the first to apply dialysis to a living organism and to use the term "artificial kidney." In Germany, Georg Haas first used the artificial kidney to dialyze a human in 1924.[6] His

attempts were only marginally successful because toxicity from his crude anticoagulant limited his ability to prolong flow in the extracorporeal circuit.

In view of these previous failures, it was not at all certain in 1944 that Willem Kolff's use of extracorporeal dialysis as a human life-saving treatment for patients with kidney failure would be successful. Three major advances aided his efforts in the nearly 20 years since Hass's work: the invention of cellophane, the discovery of antibiotics, and the availability of heparin as an anticoagulant. Through his keen interest in kidney failure and his aptitude for mechanics, Kolff and his patients ultimately met with success.[3] Kolff is often called the "Father of hemodialysis" because his method became accepted as the standard for temporary replacement of kidney function in patients with short-duration acute kidney failure.[7,8]

Attempts to apply hemodialysis to patients who had more prolonged or permanent loss of kidney function were limited because the artery and vein used for blood access had to be tied off after each treatment. In 1960, Belding Scribner, working with Quinton and Dillard at the University of Washington in Seattle, developed a blood access device for repeated dialysis using plastic tubes inserted into the artery and vein.[9] This device, known as the Scribner shunt, and the more permanent arteriovenous (AV) fistulas later introduced by Brescia and Cimino allowed hemodialysis to be repeated for many years as a life sustaining treatment.[10] For their pioneering work in the field of artificial organs, Kolff and Scribner were granted the prestigious Lasker Clinical Medical Research Award in 2002.[11]

Kidney Replacement Therapy

Available Modalities

After the success of hemodialysis, other forms of extracorporeal kidney replacement were attempted, including *hemofiltration* and *hemodiafiltration*. These methods rely primarily on convective filtration of the blood instead of diffusion. Several forms of intracorporeal dialysis were attempted, including dialysis of the pleura and pericardium, diarrheal therapy, and dialysis of loops of bowel, but the most successful intracorporeal modality has been peritoneal dialysis. The most promising replacement therapy is kidney transplantation because it can restore normal or near-normal kidney function, including potential functions not yet discovered, with the least inconvenience to the patient.

Hormone Replacement

Modern studies of kidney physiology show that the kidney, like other body organs, has an endocrine function, which means that it produces hormones that act on distant organs.[12] Currently recognized nephrogenic hormones include erythropoietin, thrombopoietin, calcitriol, prostaglandins, and renin. A better understanding of renal endocrinology and availability of the hormones has allowed dialysis providers to replace erythropoietin and calcitriol, both deficient in patients with kidney failure. More recent advances include the development of longer acting forms of erythropoietin and development of calcitriol analogs and calcimimetic drugs with more specific suppressive effects on secretion of parathyroid hormone. A large prospective, double-blinded, and randomized controlled trial is in progress to evaluate whether administration of growth hormone to adult hemodialysis patients with low serum albumin will improve survival, reduce morbidity, and improve health.[13] See Chapters 7 and 9 for further discussion of hormone replacement.

Psychological Support

The patient's initial depression on learning about failure of the kidneys; the subsequent denial, often followed by anger and rejection of medical and surgical treatments; and the negative attitude toward replacement therapy are expected responses that are more intense in younger patients. These psychological reactions to kidney failure and dialysis are undergoing active investigation using quality of life measures developed specifically for dialysis patients and various depression screening measures.[14,15] An estimated 25% to 44% of dialysis patients suffer from depression.[14–16] Poor quality of life and persistent depression are associated with higher levels of comorbidity, including malnutrition, anemia, poor quality of sleep, delayed initiation of dialysis, low level of physical function, presence of inflammation, and impaired immune function,[14,15,17–20] hospitalization,[21,22] and death.[14,21,23–25] Despite the significant morbidity and mortality associated with depression, less than 20% of depressed patients received treatment.[16] Additional studies are needed urgently to determine the optimal treatment and its impact, if any, on mortality.

Prevention and Management of Medical Complications

Successful management of hemodialysis-dependent patients requires anticipation and prevention of problems rather than simply reacting to crises. Current approaches include attempts to reverse the psychological effects of kidney loss as discussed previously, preventing anemia and bone disease, monitoring the patient for signs of malnutrition, monitoring the function of peripheral AV access devices, expecting hypotension during dialysis in patients with concentric ventricular hypertrophy, adjusting medication doses appropriately, and monitoring the quality of dialysate water. Water quality is especially important because the patient is exposed to large volumes that may contain toxic substances, such as aluminum or bacterial endotoxin (see Chapters 23 and 24). Several recent publications documenting higher hospitalization rates,[26] morbidity,[27,28] and mortality[29–31] in patients with chronic kidney disease referred late to nephrologists have highlighted the importance of preemptive care in patients approaching end stage. Clinical practice guidelines and practical recommendations have been published and are now available in several countries, each with the ultimate goal of improving the quality of life for dialysis patients.[32–35]

Definitions

Dialysis is the passage of molecules in solution by *diffusion* across a *semipermeable membrane*. Essential elements of this process are the *solvent* containing dissolved *solutes*, and the

membrane that contains pores through which some or all of the solutes move by diffusion (Figure 20-1, A). The molecular kinetics of diffusion are both solute- and membrane-specific. Solute characteristics that affect movement across a particular membrane include its concentration, molecular weight, shape, charge, and lipid solubility. Membrane characteristics that determine permeability to a particular solute include the average effective pore size; the number, geometry, and distribution of pores within the membrane; membrane surface area and thickness; and surface characteristics, such as charge and hydrophilicity. The solvent itself may also move by diffusion if its chemical activity is not balanced across the membrane. Although solutes may move in both directions across the membrane, it is customary to refer to the compartment containing more vital substances that one wishes to preserve as the *dialyzed compartment* and to the solution in the other, usually larger, compartment as the *dialysate*.

The concept of molecular diffusion is critically important to the definition of dialysis. Solutes pass through the membrane down an electrochemical gradient caused primarily by a difference in concentration across the membrane (see Figure 20-1, A). This concentration gradient, which is the driving force for diffusion, may also be dissipated by the dialysis (i.e., the molecular concentration gradient tends to fall with dialysis).

In the absence of an electrochemical gradient, solutes may also pass through pores in the membrane by *filtration*, a process of convection. The driving force for filtration is *pressure*, either hydraulic or osmotic, that is unbalanced across the membrane (Figure 20-1, B) and independent of dialysis. During filtration, solute passively accompanies the solvent from one compartment to the other, causing no change in solute concentration. Convective movement may occur in the opposite direction to diffusive movement, and, even in the same direction, convective movement may interfere with dialysis (i.e., the two fluxes may not be additive when they occur simultaneously).

Hemodialysis means literally "dialysis of the blood." This form of dialysis is distinguished by its location outside the body and by the continuous flow of blood across the dialyzer membrane. Therapeutic hemodialysis is most often used to treat kidney failure by equilibrating the blood against an isoosmotic dialysate. Vital solutes are added to the dialysate

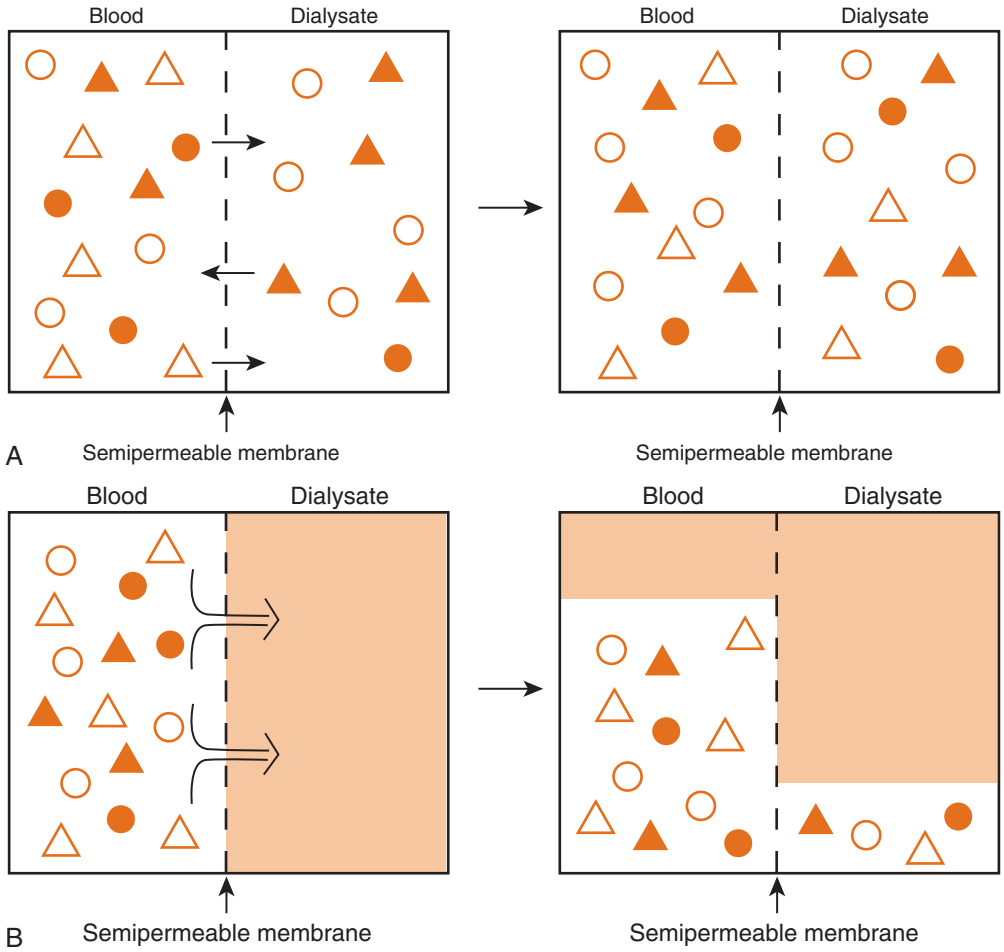


FIGURE 20-1 A, Diffusion across a semipermeable membrane. Solutes with higher concentrations in the blood compartment, such as potassium (*solid circles*) and uremic toxins (*open triangles*), diffuse through the membrane into the dialysate compartment. Conversely, solutes with higher concentration in the dialysate, such as bicarbonate (*closed triangles*), diffuse into the blood compartment. Solutes such as sodium and chloride (*open circles*), with concentrations nearly equivalent in the two compartments, move little across the membrane. B, Convection across a semipermeable membrane. Hydrostatic pressure applied to the blood compartment causes the solvent to flow across the membrane into the dialysate compartment, bringing along solutes. As a result, for solutes with a sieving coefficient close to 1, there is no change in concentrations in the blood compartment with time.

TABLE 20-1 Solutes Present in Dialysate

COMPONENT	CONCENTRATION (mEq/L)
Sodium	135-145
Potassium	0-4
Chloride	102-106
Bicarbonate	30-39
Acetate	2-4
Calcium	0-3.5
Magnesium	0.5-1
Dextrose	11
pH	7.1-7.3

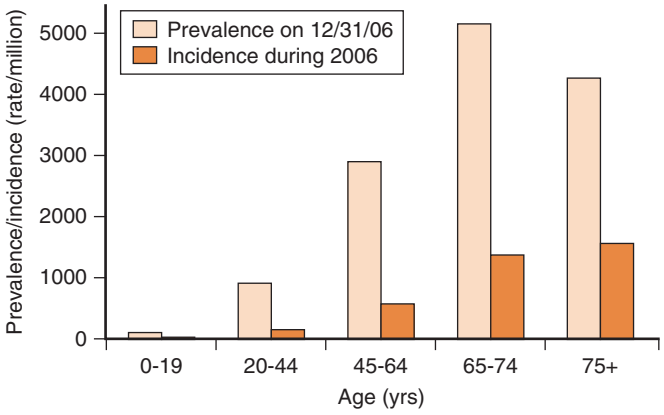


FIGURE 20-2 Prevalence and incidence of ESRD with age. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S1-S374.)

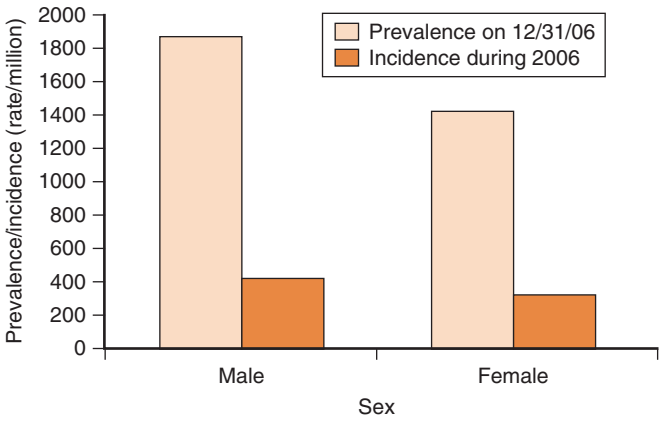


FIGURE 20-3 Prevalence and incidence of ESRD with sex. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney. Dis. 53 [Suppl 1] [2009] S1-S374.)

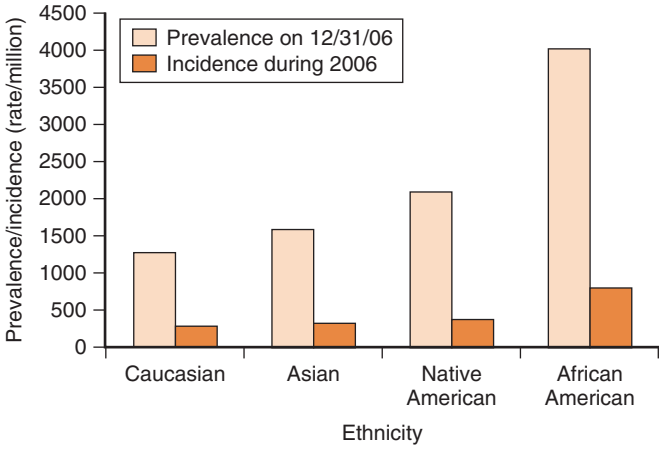


FIGURE 20-4 Prevalence and incidence of ESRD with ethnicity. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S1-S374.)

at concentrations designed to mimic those normally maintained in the blood by the native kidney (see Figure 20-1, A; Table 201). The resulting dialysate is essentially a physiological salt solution that, in addition to creating a gradient for removal of unwanted solutes, reproduces another vital function of normal kidneys, that of maintaining a constant physiological concentration of extracellular electrolytes.

Demographics

According to the Centers for Medicare and Medicaid Services, at the end of 2006, there were 506,256 patients in the United States with end-stage renal disease (ESRD).[36] Of these ESRD patients, 30% had functioning transplants and the remainder were maintained by dialysis. Both the prevalence and the incidence of ESRD vary greatly with age (Figure 20-2). The high incidence to prevalence ratio reflects a high mortality rate, especially in older age groups. The incidence rate is higher for men (451/million) than for women (289/million) (Figure 20-3), and the disease shows an ethnic predilection for African Americans and Native Americans (Figure 20-4). The causes of ESRD are listed in Table 20-2. Since 1980, the percentage of patients with diabetic kidney disease has increased from near 0% to 45% of patients initiating dialysis in 2006, primarily because of increased acceptance of diabetic patients into dialysis programs. Today the mortality rate remains higher than the average, but diabetes mellitus has become the most common cause of ESRD (see Table 20-2).[36] Mortality rates for patients with diabetic kidney disease also rise with age, but a higher mortality rate is apparent in younger type I patients with diabetes, as shown in Figure 20-5.

The cause of the high ESRD mortality documented in the United States, compared to other countries, is controversial.[37] Speculation ranges from delivery of relatively inadequate dialysis or more liberal acceptance of patients in the United States to inadequate records of mortality kept in other countries. The survival of dialysis patients in the United States has slowly improved in the last 20 years, despite increasing comorbidity, but remains greater than 20% per year in the first 2 years after starting dialysis. Statistics from the United States Renal Data System (USRDS) for patients starting dialysis in 2000 through 2001 show a 79% 1-year survival, 65% 2-year survival, and 38% 5-year survival (Figure 20-6).[36] Causes of death[36] are listed in Table 20-3. Greater than 50% are due to cardiovascular disease, but it is unclear whether the uremic milieu, coexisting medical illnesses, or dialysis itself accounts for the high mortality

TABLE 20-2 Causes of End-Stage Renal Disease in Incident and Prevalent Patients in the United States in 2006

PRIMARY RENAL DISEASE	INCIDENT PATIENTS N	INCIDENT PATIENTS % TOTAL	PREVALENT PATIENTS N	PREVALENT PATIENTS % TOTAL
Diabetes mellitus	49,224	44.5	188,381	37.2
Hypertension	29,662	26.8	122,339	24.2
Glomerulonephritis	7982	7.2	80,164	15.8
Cystic kidney disease	2651	2.4	23,685	4.7
Urological disease	1670	1.5	13,371	2.6
Other known cause	13,756	12.4	52,989	10.5
Unknown cause	4834	4.4	19,930	3.9
Missing cause	1075	1	5397	1.1
All ESRD	110,854	100	506,256	100

(Data from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S122-S369.)

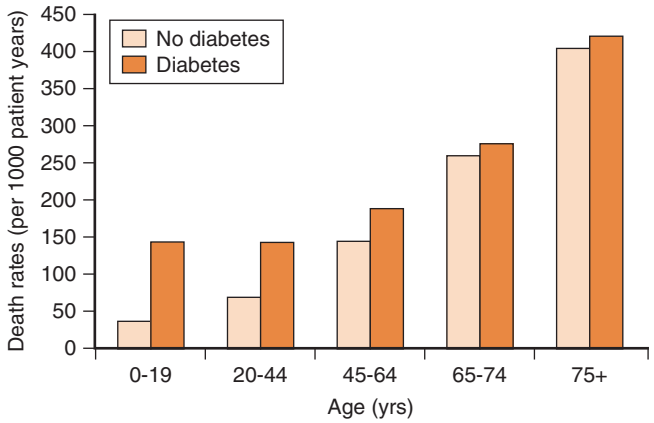


FIGURE 20-5 Mortality rates for diabetic and nondiabetic patients vary with age. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney. Dis. 53 [Suppl 1] [2009] S1-S374.)

TABLE 20-3 Causes of Death for Hemodialysis Patients Ages 45 to 64 by Diabetes Status (2004-2006)

CAUSE OF DEATH	MORTALITY (RATES PER 1000 PATIENT YRS AT RISK) DIABETES	NO DIABETES
Cardiovascular disease	95.1	61.3
Cardiac arrest	50	33.1
Acute myocardial infarction	14.5	7.8
Cerebrovascular	9.9	5.8
Other cardiac	20.7	14.6
Infection	26.7	19.7
Malignancy	3.7	8.3
Withdrawal from dialysis	7.5	4.5
Other known causes	54.7	49.7
Unknown	<0.05	<0.05

(Data from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S122-S369.)

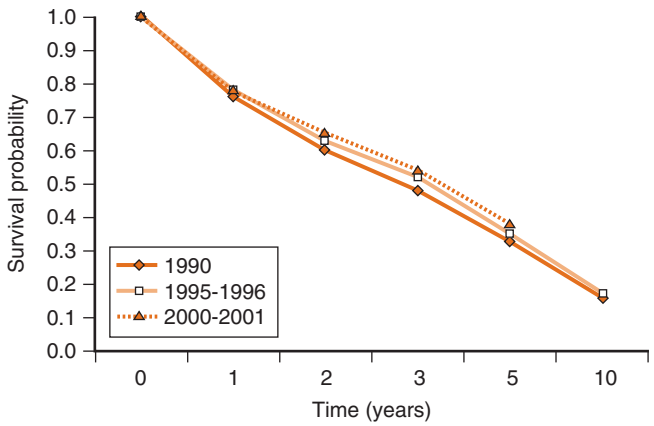


FIGURE 20-6 Probability of survival for hemodialysis patients has improved slightly over the past 10 years. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S1-S374.)

(see Chapter 10). Twenty-four percent of deaths in the United States occurred after voluntary withdrawal of dialysis because of failure to thrive, intervening medical complication, or the patient's quality of life was not sufficient to justify its continuation.[36]

As shown in Figure 20-7, the incidence of ESRD in the United States has steadily increased,[36] most likely as a result of aging of the population and increasing acceptance of dialysis for older patients as part of their Medicare entitlement. Although prior USRDS data suggested a leveling off in the rate of rise in the incidence (growth of less than 1% per year), the most recent data for 2006 suggest that the incidence may be rising again, with a growth rate of 2.1% over the preceding year (see Figure 20-7).

UREMIA: THE TARGET OF HEMODIALYSIS

Uremia is the clinical state or syndrome that is reversed by dialysis therapy, and it literally means "urine in the blood." Whether or not urine output falls, all patients with uremia accumulate solutes, collectively known as *uremic toxins*. It is this accumulation of solute, the most abundant of which is urea, that justified the application of dialysis as a treatment for uremia.[6] From another perspective, the concept of uremia as a state of intoxication by substances normally eliminated by the kidney is supported by the success of therapeutic dialysis. The kidney separates large from small

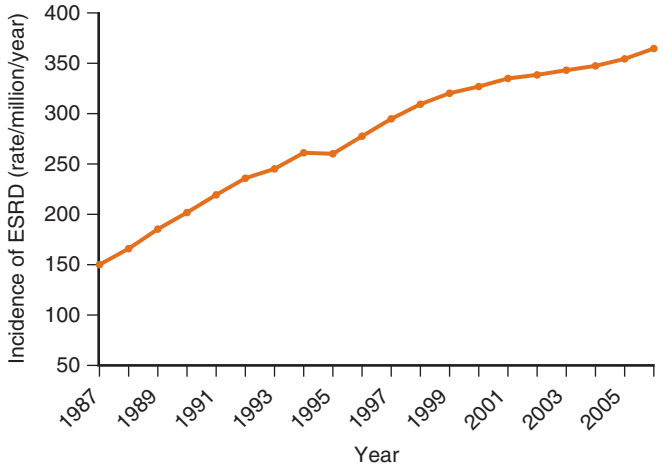


FIGURE 20-7 Incidence of ESRD in the United States with time. (Adapted from USRDS: Excerpts from the United States Renal Data System 2008 Annual Data Report, Am. J. Kidney Dis. 53 [Suppl 1] [2009] S1-S374.)

solutes by filtration, powered by the heart and accomplishing much the same function as the dialyzer, which also depends on cardiac output to deliver solute for elimination but is not powered by the heart. Some have likened dialysis to the original elimination mechanism of organisms that evolved in the infinite "dialysate" of the primordial sea. Conserved adaptation to diffusive removal of solute might explain the marked success of therapeutic dialysis in comparison to other artificial organ replacements.[38]

Clinical Syndrome

Although not all patients exhibit all of the symptoms and signs of uremia, the monotony of the clinical syndrome in patients with widely divergent causes of kidney failure indicates that the syndrome is the consequence of the kidney failure itself, not the underlying disease. Nearly every organ system is involved, but the most highly targeted are the gastrointestinal tract and the central nervous system. Early symptoms include dysgeusia, loss of appetite, nausea, weight loss, inability to concentrate on a mental task, lethargy, daytime sleepiness, pruritus, and menstrual irregularity in women. Unfortunately, these symptoms are not specific and are sometimes mistaken for an unrelated infection. They appear in most patients only at an advanced stage of kidney damage (80% to 90% loss of nephrons). Far advanced symptoms and signs include uremic serositis with pericarditis, once the harbinger of death due to uremia, central nervous system suppression leading to uremic coma, overt peripheral neuropathy, and uremic fetor due to volatile amines emitted in the breath.

Fluid accumulation, which is subtle in most patients, contributes to hypertension that eventually leads to cardiac hypertrophy and diastolic dysfunction. The latter may precipitate a visit to the emergency room for treatment of congestive heart failure. Because cardiovascular disease is the most common cause of death in hemodialyzed patients, increasing attention has been focused on this aspect of the uremic syndrome and on blood pressure and other risk factors for cardiovascular complications, especially in the early phases of Chronic Kidney Disease (CKD) (see Chapter 10).

Uremic Toxins

The most life-threatening solutes known to accumulate in uremia (Table 20-4) are low in molecular weight and consequently are dialyzable. Some originate from food (e.g., sodium and phosphorus), whereas others are products of metabolism (e.g., urea, uric acid, and hydrogen ion) or gut flora (e.g., phenols and indoles). Routine clinical measurements include sodium, potassium, bicarbonate, chloride, urea, creatinine, uric acid, magnesium, calcium, phosphate, intact parathyroid hormone, serum bicarbonate as an inverse marker of acid accumulation, and sometimes aluminum and β_2-microglobulin levels. Outside of these readily available solute levels, serum levels of the other solutes in Table 20-4 are not clinically useful.

Although urea is a poor marker of native kidney function, it has special significance in ESRD patients because it is the most abundant solute to accumulate and because its accumulation results from both amino acid catabolism and failure of renal excretion. Because urea generation is an index of protein nutrition, monitoring urea levels is potentially doubly important. However, this dual origin of urea complicates interpretation of any single measured level, rendering it nearly useless unless additional measurements are taken to determine the relative contributions of generation and excretion. Mathematical models of urea kinetics applied to serum urea concentrations measured before and after dialysis treatments allow separation of amino acid catabolism from the contributions of dialyzer and native kidney function. As discussed in more detail subsequently, this modeling process currently forms the basis for quantifying and prescribing hemodialysis (see Quantifying Hemodialysis).

A host of other substances have been shown to accumulate in renal failure, but data on their potential toxicity are sparse. As the list of uremic retention solutes grows steadily, approaches to analyze these solutes more systematically are underway, and the realization that a significant number of uremic retention solutes may not be amenable to removal with conventional dialysis is dawning (Figure 20-8).[39–42] Proposed uremic toxins can be grouped according to the following characteristics that influence their removal with dialysis to allow exploration of novel ways of removal when dialysis is not successful:[39–42]

- Water-soluble, low-molecular weight solutes
- Protein-bound solutes
- Sequestered solutes
- Middle to large molecules

Some of these substances are carbamylated proteins from posttranslational modification by high concentrations of urea and cyanate, advanced glycation end products from the Maillard reaction between 3-deoxyglucosone and the terminal NH2 groups of proteins, β_2-microglobulin, p-cresol sulfate, parathyroid hormone, hydrogen ion and metabolic acidosis, homocysteine, other organic and phenolic acids, advanced lipoxidation end products, and advanced oxidation protein products.[39,41–52] Some of these substances have been linked with specific diseases:

TABLE 20-4 Solutes That Accumulate in Uremia and Their Proposed Toxicity (If Known)

SOLUTE	PROPOSED TOXICITY
Free water-soluble low-molecular-weight	
Sodium	Volume overload
Potassium	Arrhythmia, muscle weakness
Hydrogen ion (metabolic acidosis)[49]	Degrades protein (activates ubiquitin proteasome); alters vitamin D and parathyroid hormone levels
Urea	None
Creatinine	None
Guanidines[42,52]	Immune dysfunction; neurotoxicity
Oxalate[52]	Tissue deposits; inhibits endothelial cell replication and migration
Asymmetrical dimethylarginine[281]	Cardiovascular disease; inhibits inducible nitric oxide synthase
3-carboxyl-4-methyl-5-propyl-2-furanproprionic acid[52]	Displaces drugs bound to albumin; inhibits erythropoiesis; inhibits mitochondrial oxidation
4-hydroxybenzoic acid (phenolic acid)[52]	Platelet dysfunction; shortened red cell survival; neurological symptoms
Protein-bound	
Hippuric acid[52]	Muscle weakness; neurological symptoms; decreases drug binding to albumin
Indoxyl sulfate[41,42,52]	Displaces drugs bound to albumin; oxidative stress; cardiovascular disease
p-cresol[41,42]	Immune dysfunction; cardiovascular disease; oxidative stress
Quinolinic acid[52]	Inhibits erythropoiesis; seizures in mice
Homocysteine[50]	Cardiovascular disease
Pentosidine[282]	Cardiovascular disease
Leptin[42]	Cardiovascular disease
Sequestered	
Phosphate	Osteodystrophy; cardiovascular disease
Magnesium	Muscle weakness
Middle (500-5000 Dalton) and high (5000-50,000 Dalton) molecular weight	
Parathyroid hormone[47,48]	Inhibits mitochondrial oxidation; hypertrophic cardiomyopathy; cardiac fibrosis; immune dysfunction
β_2-microglobulin[44,46]	Dialysis amyloidosis
Carbamylated proteins[43]	? Cardiovascular disease
Advanced glycation end products[42,44,45]	Dialysis amyloidosis; cardiovascular disease; oxidative stress

- β_2-microglobulin and advanced glycation end products with amyloidosis[44,46]
- Advanced glycation end products, parathyroid hormone, p-cresol sulfate, and indoxyl sulfate with heart disease[41,42,45,47,48]
- Phenolic acids, dicarboxylic acids and guanidines variably with inhibition of erythropoiesis, shortened red blood cell life span, and neurological symptoms in animals[52–54]
- Both phenolic acids and dicarboxylic acids with impaired protein binding of drugs[52,55]
- Advanced lipoxidation end products and advanced oxidation protein products with atherosclerosis[39,41,42]

These substances are thought to evoke their toxicity by 1) progressive bulk accumulation (e.g., β_2-microglobulin and advanced glycation end products), 2) upsetting the oxidation-reduction balance (e.g., *p*-cresol sulfate, indoxyl sulfate), 3) binding to vital signaling and transport proteins (e.g., phenolic acids), 4) altering second messengers, and 5) altering nitric oxide production.[56,57]

Despite its importance as a measure of dialysis adequacy, urea itself has demonstrated little toxicity in experiments where urea was added to the dialysate to prevent its removal.[57,58] Similarly, although all other solutes mentioned accumulate in patients with kidney failure, their levels are well below that necessary to evoke toxic responses in animals and in humans, even when measured in patients with ESRD.[39,40] Even after decades of research, investigators are unable to identify a single toxin or a group of toxins responsible for the immediate life-threatening uremic syndrome that is quickly reversed by dialysis.[39,59,60] Because dialysis does little more than remove fluid and dialyzable solutes, the uremic syndrome must result from accumulation of known and unknown toxins in aggregate, perhaps each at subtoxic levels.

Residual Syndrome

It is now clear that the amount of dialysis necessary to sustain life is not enough to maintain a high quality of life. A challenge to current investigators is the development of techniques for analyzing and treating this "residual syndrome," which affects some patients more than others but reduces the quality of life despite apparently adequate dialysis.[39,60] At present, several components of the syndrome can be identified, such as anemia, osteodystrophy, dialysis

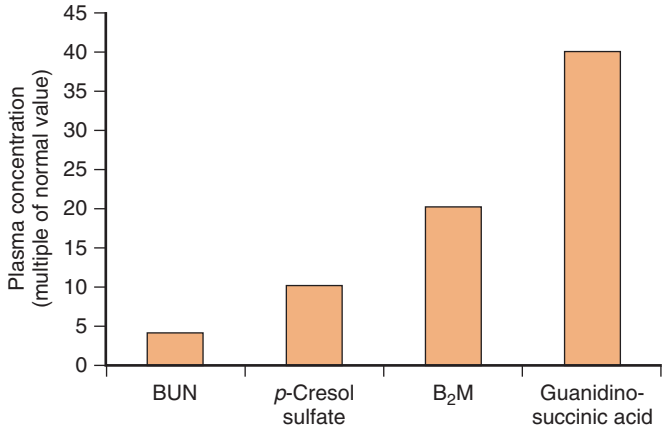


FIGURE 20-8 Effect of protein-binding, molecular weight, and sequestration on solute concentrations in hemodialysis patients. Conventional thrice weekly dialysis removes blood urea nitrogen (BUN) effectively, rendering the average urea level in a hemodialysis patient about four times the normal value. Binding of p-cresol to albumin and the large molecular size of β_2-microglobulin limit the ability of conventional dialysis to remove them. Thus their levels are about 10 to 20 times those of normal, respectively. Plasma guanidinosuccinic acid levels are even higher at 40 times than of normal because of increased production in kidney failure and sequestration within cells, thereby limiting its removal during dialysis. Although plasma levels of solutes other than urea are several orders of magnitude higher than normal, their absolute levels are much lower than those of urea. In addition, it is unclear whether they exert any toxicity or are simply retained because of kidney failure. (Adapted from Meyer, et al: N Engl J Med 2007;)

amyloidosis, accelerated atherosclerosis, anorexia, disordered sleep, and fatigue, some of which are treatable (see Chapters 7–10, 12, 13, 16, and 18). The proposed uremic toxins discussed previously may account, in part, for the residual syndrome, but almost certainly, other components remain to be defined.[39,41,42,57,60] These components include 1) the cause of inflammation in dialysis patients;[61–64] 2) the cause of malnutrition and accelerated atherosclerosis;[65–68] 3) the role of hyperhomocysteinemia in accelerated atherosclerosis[50,51] and graft thrombosis;[69] 4) the role of hyperphosphatemia in cardiovascular disease;[70–74] 5) the interaction among malnutrition, inflammation, and atherosclerosis;[66–68] and 6) the role of endothelial dysfunction as a mediator of cardiovascular disease.[75–78] A complete understanding of the basis for the residual syndrome remains elusive, but extensive uncontrolled experience with more frequent dialysis suggests that control of small solutes is less than optimal when treatments are limited to three per week. The Hemodialysis (HEMO) study (see later Goals of Hemodialysis) showed that increasing the clearance while limiting the frequency has little or no effect on outcomes, a prediction supported by solute kinetic analysis (see later Solute Disequilibrium).[79] Other proposed underlying causes of the residual syndrome include accumulation of toxins that are poorly dialyzable because of their larger molecular size,[42] protein-binding in the blood or tissues,[39,41,42,55] or sequestration with slow release from compartments other than the blood.[80–82] More recent studies indicate that the clearance of some protein-bound solutes can be substantially increased by increasing both dialyzer surface area and dialysate flow but not by hemofiltration.[55,83] Increasing the frequency of dialysis to 6 days per week may also improve the removal of larger or sequestered molecules.[84–86] Addition of binding agents to the dialysate has also proven effective, but the ultimate effect on patient outcome remains uncertain.[87]

Goals of Hemodialysis

The primary goal of hemodialysis is the replacement of kidney excretory function. There is no doubt that hemodialysis can sustain life in patients who have no kidney function. Survival for as long as 30 years has been documented for hemodialysis alone, a treatment that does nothing more for the patient than remove solute.[88] Moreover, the molecular weight range of effectively removed solutes was relatively low until recent years when high-flux dialysis membranes were introduced.[89] The earlier experience indicates that the most life-threatening toxins are easily dialyzable. Precise goals and standards of dialysis adequacy have been defined, based on outcome studies in large populations, in terms of the clearance of small-molecular-weight, easily dialyzed solutes, the marker for which is urea.[32–35]

A prospective interventional study of dialysis adequacy in the late 1970s, the U.S. National Cooperative Dialysis Study (NCDS), provided clear-cut evidence for a level of urea clearance that was inadequate (see Chapter 22).[90] Later uncontrolled experience suggested that more dialysis might be better for the patient (see Chapter 22).[91–94] Analysis of solute kinetics, however, shows that the benefit of dialysis is logarithmically related to the dose and that, depending on the frequency of treatments, a point is reached beyond which more dialysis does nothing more than inconvenience the patient, potentially worsening the quality of life.

This theoretical construct was confirmed recently by the National Institutes of Health (NIH)-sponsored HEMO Study, a multicenter prospective clinical trial that randomized 1846 patients to receive thrice weekly hemodialysis with a target equilibrated Kt/V of 1.05 (equivalent to single pool Kt/V of 1.25, the generally accepted minimal standard at the time of the study) versus 1.45 (equivalent to single pool 1.65) (see Chapter 22).[79] For now, hemodialysis patients should receive a urea clearance (spKt/V) of at least 1.2. Based on favorable results of observational studies and mathematical constructs, an ongoing NIH sponsored clinical trial is currently testing the effects of more frequent hemodialysis on patient outcomes.[95,96] Whether more frequent dialysis in the form of daily short-duration hemodialysis or daily nocturnal hemodialysis will reduce further mortality or morbidity remains to be determined.

A secondary goal of hemodialysis treatment is the replacement of hormones normally produced by the kidney. Even before dialysis therapy was available, the devastating effects of vitamin D "resistance" were evident, and much was written about renal rickets in children and osteomalacia in adults. When 1,25-dihydroxyvitamin D (calcitriol), an activated form of vitamin D, was isolated in 1969 from renal proximal tubular cells, where it is formed from the precursor 25-hydroxyvitamin D, the puzzle was solved.[97] The subsequent synthesis of calcitriol allowed clinical nephrologists to replace this vital hormone[98] and prevent renal osteodystrophy, one of the most devastating long-term complications of kidney failure (see Chapters 8 and 9).[99]

Increasing availability of calcitriol analogs and calcimimetics has further enhanced the nephrologist's ability to suppress parathyroid hormone levels while preventing hypercalcemia.[100] Ongoing efforts are aiming to develop the optimal regimen for long-term prevention of soft tissue calcification and ossification.[74,100–103]

In contrast to bone disease, there was less mystery about the anemia of kidney failure, which was a recognized effect of deficient erythropoietin, a hormone uniquely synthesized by the kidney and responsible for activation of bone marrow erythroid precursors.[104,105] Even before dialysis is necessary, hemoglobin levels begin to decline, causing a syndrome of anemia that has subtle adverse effects on multiple organ systems.[106–108] The synthesis and widespread availability of erythropoietin in the late 1980s and early 1990s removed the transfusion dependency for nearly all patients and improved the quality of life for most patients by raising the average blood hemoglobin concentration (see Chapter 7).

In addition to the need for dialysis, patients require extensive psychological and social services support to cope with their own emotional reactions to loss of a vital organ. Nutritional counseling is also important, primarily to limit fluid gains between dialyses, to control hyperphosphatemia (phosphate is removed poorly by standard hemodialysis), to reduce the life-threatening risk of hyperkalemia, and to prevent malnutrition (a major yet potentially reversible risk for morbidity and mortality). Successful treatment and rehabilitation of the whole patient requires intensive initial emotional support and prolonged surveillance of the patient's nutrition.

DIALYSIS

As defined previously, dialysis is a process of diffusion of molecules in solution across a semipermeable membrane. Forces that govern the pattern and rate of diffusion have been defined in precise mathematical terms that include properties of the molecule, the solvent, and the membrane. The salient points of the physics applicable to dialysis are discussed here because a detailed analysis is beyond the scope of this chapter. For detailed analysis of the physical laws that govern dialysis, the reader is referred to formal texts on kinetic modeling.[109–111]

Laws of Diffusion

Diffusion is a consequence of random molecular movements (molecular kinetics) that follow the laws of probability and are driven by temperature, pressure, and concentration. Because temperature and pressure are relatively constant during therapeutic dialysis and among dialysis centers (see later text), the major clinical variable that affects diffusion is the solute concentration. Fick law of diffusion, derived from mathematical laws of statistical probability, shows that the rate of diffusion is linearly dependent on the *concentration gradient* (i.e., the driving force for diffusion):

$$(1) \qquad -J = (DA/X)\Delta C$$

J is *solute flux* (mg/min), which, when applied to a membrane, can be viewed as the unidirectional rate of movement of a solute across the membrane (see Figure 20-1). ΔC is the concentration gradient across the membrane (mg/ml), A is the membrane area (cm^2), X is the membrane thickness (cm), and D is a constant, called the *coefficient of diffusion* or diffusivity (cm^2/min). The last-mentioned is a measure of the permeability of the membrane material to the measured solute, independent of solute concentration, area, and thickness. Conventionally, a minus sign is placed on the left side of Equation 1 to indicate that solute moves away from the dialyzed compartment (opposite to the direction of the gradient). Equation 1 reflects the intuitive concept that diffusion across a membrane varies directly with the membrane area and solute concentration gradient and inversely with the membrane thickness.

Dividing both sides of Equation 1 by ΔC results in an expression for *solute dialysance*:

$$(2) \qquad -J/\Delta C = \text{dialysance} = DA/X$$

Equation 2 shows that dialysance is always independent of concentration and is constant throughout a static dialysis despite changes in concentration on both sides of the membrane. Clinicians rarely use the concept of dialysance, opting instead to describe dialysis in terms of *clearance*. This is reasonable because clearance is derived from measurements only on the blood side of the membrane where solute concentrations are easily measured. The only difference between dialysance and clearance is the substitution of blood side C for ΔC in Equation 2:

$$(3) \qquad -J/C = \text{clearance} = K$$

When the concentration of solute on the dialysate side is zero, ΔC = C, and clearance is equal to dialysance. This condition exists at the start of a dialysis procedure and during all therapeutic single-pass dialyses (see Hemodialysis). For all other conditions, ΔC is less than C, so clearance is lower than dialysance.

If the *volume of the dialyzed compartment* (V) is constant, dividing both sides of Equation 3 by V shows that the fractional rate of change in concentration is constant:

$$(4) \qquad -(J/V)C = K/V = k$$

The symbol k is called the *rate constant*. The constantly changing term J/V, when expressed at any given instant, is dC/dt and therefore (J/V)/C is (dC/C)/dt. The latter can be viewed as the fractional change in concentration over an initial short period of time (dt):

$$(5) \qquad -(dC/C)/dt = K/V = k$$

Equation 5 demonstrates that concentration-dependent diffusion is a *first order process*; that is, despite the minute-to-minute changes in concentration within the dialyzed compartment, the fractional rate of change is constant when the dialysate concentration remains zero. Flux of solute across the membrane, which is the goal of dialysis, is both driven by the concentration and expressed as a change in concentration. When the rate of change is factored by the driving force [(dC/dt)/C)], the resulting fractional rate of change is constant.

The rate constant (k) in Equation 5 has units of $time^{-1}$ or a fraction per unit of time and is a function of both the molecular properties of size, shape, charge, and interaction with the membrane, and of the membrane itself, including its surface area, porosity, and thickness. Large molecules, those with complex shapes, and those with an electrical

charge diffuse less readily across the membrane. Membranes that are more porous, have larger surface, and are thinner favor passage of solutes by diffusion. Although the rate constant is useful to demonstrate the first order concept, it has less practical value than the expression for clearance depicted in Equation 3.

The difference between the rate constant (k) in Equation 4 and the clearance (K) shown in Equation 3 is V, the volume of solute distribution. Equation 3 has the advantage of expressing the dialysis effect as a volume equivalent of solute diffusing across the membrane per unit of time. The volume transferred per unit of time is constant; that is, a milliliter equivalent of solute is transferred per unit of time regardless of how much solute is contained in that milliliter. The rate of diffusion is directly proportional to the membrane surface area, which is constant for any given model of dialyzer.

Effects of Temperature, Pressure, and Molecular Weight

Diffusion is a consequence of molecular motion, which is affected by pressure and heat energy and by molecular mass. The rate of diffusion is proportional to the absolute temperature, which is approximately 273°K at room temperature. Within the range of temperatures experienced in the dialysis center, the proportionate change in absolute temperature (260° to 280°K) is so small that its influence on diffusion across the dialysis membrane is negligible. More important are the physiological effects of temperature on blood flow and body water compartmentalization, which have significant effects on solute kinetics within the patient (see Quantifying Hemodialysis). Similarly, pressure effects have little influence on diffusion within the range of pressures recorded in modern dialyzers.

Molecular mass plays a more significant role in determining the rate of diffusion, because at a given temperature and pressure, the heavier molecules move more slowly and collide with the semipermeable membrane less frequently. Small-molecular-weight substances, such as urea and creatinine, diffuse readily across a semipermeable membrane, whereas larger substances, such as β_2-microglobulin or albumin, diffuse slowly or not at all. The larger size of the heavier molecules further impedes diffusion through small pores.

Dialysate

Preparation of the dialysate and its composition are critical to the success of dialysis. For hemodialysis, the solution must be prepared from properly treated water (see Chapter 24) and contain the solutes listed in Table 20-1 in concentrations comparable to those of plasma. Dialysate must have a low concentration of endotoxin to prevent pyrogen reactions in the patient, but, in contrast to peritoneal dialysate (see Chapter 27), sterility is not a requirement because the semipermeable membrane excludes large particles, such as bacteria and viruses. Vital electrolytes and glucose are added to the dialysate to reduce or abolish their concentration gradients, whereas bicarbonate or a bicarbonate precursor is added in higher concentrations to promote accumulation in the patient. Dialysate glucose concentrations are near those of plasma; thus in contrast to peritoneal dialysis, osmotic forces do not play an important role in removing fluid.

In practice, solute concentrations in the dialysate are fairly standard. The most common concentrations that may be individualized are those for potassium, calcium, and bicarbonate (see Table 20-1). In many dialysis centers, the bicarbonate concentration is fixed at 35 or 39 mEq/L. Potassium ranges from 0 to 4 mEq/L, depending on the patient's serum concentration before dialysis. A compelling reason must exist, however, to use dialysate potassium concentrations of 0 or 1 mEq/L because of the dangers associated with a precipitous drop in the serum concentration. In particular, patients on digoxin must be dialyzed against at least 2 mEq/L of potassium. Calcium concentrations vary from 1 to 3.5 mEq/L. At the lower concentration, calcium is removed from the patient, whereas at the higher concentration, calcium diffuses into the patient during dialysis. The concentration of sodium is usually fixed at 140 mEq/L, which is the middle of the normal range in whole plasma.

HEMODIALYZERS

A hemodialyzer, synonymous with a dialyzer, is often called an "artificial kidney." It is configured to allow blood and dialysate to flow, preferably in opposite directions, through individual compartments, separated by a semipermeable membrane. By convention, blood entering the hemodialyzer is designated *arterial*, whereas blood leaving the hemodialyzer is *venous*. The principal differences among the many available hemodialyzers are the membrane composition, membrane configuration, and membrane surface area. Hemodialyzers affect the efficiency and the quality of dialysis by virtue of their membranes, which determine their K_OA value, and by the rates of blood and dialysate flow, which determine their clearance values (see later discussion of K_OA) (Table 20-5).

TABLE 20-5 Key Factors That Affect the Solute Clearance of a Hemodialyzer

Properties of the membrane
↑ Membrane porosity
↓ Membrane thickness
↑ Membrane surface area
Properties of the solute
↓ Molecular weight and size
Shape
↓ Charge
Blood side
↓ Unstirred blood layer
↑ Blood flow
Dialysate side
↓ Dialysate channeling and unstirred layer
↑ Dialysate flow
↑ Countercurrent direction of flow

↑ Increases clearance; ↓ decreases clearance

Membrane Composition, Configuration, and Surface Area

Composition of the Membrane

Two major classes of membrane material are available commercially: 1) cotton fiber, or *cellulose-based membranes*, and 2) *synthetic membranes*. Cellulose-based membranes range from unmodified cellulose to substituted cellulose membranes. Unmodified cellulose membranes have many free hydroxyl groups, which are thought to be responsible for their bioincompatibility and propensity to activate white blood cells, platelets, and serum complement. In an effort to improve membrane biocompatibility while keeping costs down, the cellulose polymer is treated with acetate and tertiary amino compounds to form a covalent bond with the hydroxyl groups (e.g., cellulose acetate and animated cellulose—Cellosyn or Hemophan). Further issues of biocompatibility are covered in detail in Chapter 24.

The major polymers in commercial synthetic membranes are polyacrylonitrile, polysulfone, polycarbonate, polyamide, and polymethylmethacrylate. Despite their increased thickness, these membranes can be rendered more permeable than the cellulose membranes, allowing for greater fluid and solute removal. They are also more biocompatible. Because the pore sizes in the synthetic membranes can be made wider, larger-molecular-weight substances, such as β_2-microglobulin, can be removed more efficiently.[112,113] High-flux synthetic membranes also clear phosphate more efficiently, although the effect on serum phosphate levels is minimal. Despite their increased cost, synthetic hemodialyzers are increasingly preferred.

Hollow Fiber Dialyzers

Current hemodialyzers are constructed with a plastic casing, usually polycarbonate that encloses several thousand hollow fiber semipermeable membranes stretched from one end to the other, imbedded at each end into a plastic *potting compound*, usually polyurethane, that serves as the headers.

The blood compartment fiber bundle volume of the *hollow fiber dialyzer* is 60 to 120 ml, which in contrast to older dialyzer designs, does not expand during dialysis. Each fiber has an inside diameter of approximately 200 μm. The potting material separates the blood compartment from the dialysate compartment where dialysate flows between and around each fiber in the direction usually opposite to blood flow. Blood flows to or from the open end of each fiber through a removable "header" attached to the blood tubing. In addition to a lower blood priming volume, the hollow-fiber design increases the area of contact between blood and dialysate, allowing for the most efficient exchange of solutes. Recent efforts to prevent loss of surface area by fiber-to-fiber contact include insertion of spacer yarns between fibers and a wavy Moire configuration of the fibers. Major disadvantages of the hollow-fiber design are thrombosis and the potting compound, which can absorb chemicals used to disinfect newly manufactured dialyzers (e.g., ethylene oxide) or reused dialyzers (e.g., formaldehyde, peracetic acid, or glutaraldehyde). These chemicals can leach slowly from the material and potentially enter the patient's blood during dialysis (see Chapter 24).

Surface Area Considerations

Most hemodialyzers have a membrane surface area of 0.8-2.1 m^2. As the area increases, solute transport, often called *efficiency*, of the dialyzer increases. To maximize membrane surface area, one can increase the length of the hollow fiber, increase the number of hollow fibers, or decrease the diameter of the hollow fiber while holding other parameters constant.[114] Each of these maneuvers, however, has undesirable effects when carried too far. Increasing the fiber length increases shear rate and magnifies the pressure drop between blood entering and exiting the dialyzer. Increased shear rate increases ultrafiltration, whereas the pressure drop decreases ultrafiltration because the transmembrane pressure (TMP) gradient dissipates at the venous end of the dialyzer. Any decrease in ultrafiltration decreases its contribution to solute clearance and offsets the potential advantage of the increased surface area. Increasing the number of hollow fibers increases the volume of extracorporeal blood and may eventually compromise hemodynamic stability. Finally, as the diameter of the hollow fiber decreases, the increase in resistance to blood flow enhances filtration and backfiltration,[115] but clotting is also enhanced. As fibers thrombose, effective surface area for diffusion decreases and solute clearances fall. Because of these adverse consequences, the minimal acceptable internal fiber diameter is 180 μm.[117] The design and geometry of the hollow-fiber dialyzer represent a delicate balance among these factors.

The composition and the thickness of the membrane varies considerably and is often more important than the surface area in determining dialyzer efficiency. In general, the thinner the membrane, the more efficient is the transport of solutes and fluid across the membrane.

Effects of Flow on Clearance

Blood Flow

Dialyzer blood flow (Q_b) is driven by a roller pump and generally ranges from 200 to 500 ml/min, depending on the type of vascular access. Blood flow influences the efficiency of solute removal (see Table 20-5).

As Q_b increases, more solute is presented per unit of time to the membrane, and solute removal increases. Urea removal rises steeply as Q_b increases to 300 ml/min, and although urea removal continues to rise as Q_b approaches 400 to 500 ml/min, the slope is less steep. For larger molecular weight substances, removal is slower and more time-dependent rather than flow-dependent because diffusion across the membrane is limited as discussed previously.

Dialysate Flow

Most dialysis equipment generates a *single pass* of dialysate; that is, the dialysate is discarded after one passage through the dialyzer. For sorbent dialysis, however, only about 5 L of water are used and dialysate is constantly regenerated by cycling through a cartridge system to remove the undesirable solutes (e.g., urea, creatinine, and potassium).

Countercurrent flow maximizes the concentration gradient between blood and dialysate throughout the length of the dialyzer (see Table 20-5). When blood flow and dialysate

flow are in the same direction *(cocurrent)*, small solute clearance decreases by about 10%.

In addition to decreasing boundary layers and streaming effects (see later discussion), increasing Q_d minimizes the accumulation of waste products in the dialysate, providing a higher solute gradient between blood and dialysate for optimal diffusion. However, even for highly diffusible solutes, the benefits progressively diminish as the dialysate flow rate is increased above the blood flow rate.

K_OA, the Mass Transfer Area Coefficient

K_OA is the product of the *mass transfer coefficient*, K_O, which has units of cm/min, and the membrane area, A. K_O is specific for a particular molecule and membrane type, including the membrane's pore size and thickness, but is independent of solute concentration and membrane surface area. It can be considered the solute flux per unit of area per unit of concentration gradient and is equivalent to D/X in Equation 2. Because solute flux per unit of concentration gradient is defined as dialysance, K_O may also be expressed as the dialysance per unit of membrane area. K_OA, which is the *mass transfer area coefficient*, therefore has units of ml/min, and is equivalent to the dialysance of a membrane with a fixed area during static dialysis (no flow). In addition to being independent of solute concentration, K_OA is also independent of blood and dialysate flow within certain limits (see later text). Therefore, K_OA is the most specific constant that describes the efficiency of a dialyzer for removal of a particular solute and is the best parameter for comparing dialyzers. Higher values indicate more efficient solute removal.

K_OA has the same units of measurement as clearance and, in practical terms, can be considered the maximum clearance achievable for a particular dialyzer and solute. Maximum clearance is achieved at the beginning of dialysis when blood solute concentrations along the length of the dialyzer are equal (no flow) and dialysate concentration is 0 or, at the opposite extreme, when blood and dialysate flow rates are infinite. Under these two conditions, the only factor governing a solute's clearance is the dialysis membrane.

Conversely, when Q_b and Q_d are finite, the clearance is lower than K_OA because both flow rates govern diffusion, as discussed previously and because of the way clearance is expressed, as the solute removal rate divided by the *inflow concentration*. The net driving force for removal is the *mean concentration gradient* across the membrane, which is a complex function of Q_b and Q_d (see next section). The increase in clearance caused by an increase in Q_b is the result of a flow-dependent increase in the mean concentration gradient across the membrane, driving more solute into the dialysate. Because the inflow concentration does not change with increased Q_b, the conventional measure of clearance as defined previously increases with increasing Q_b.

Relationships Among Flow, K_OA, and Solute Clearance

Because concentrations change logarithmically in the direction of flow along the dialyzer membrane, the true mean concentration on either side of the membrane is actually the log mean concentration expressed:

$$\text{log mean } C = (C_{in} - C_{out})/\ln(C_{in}/C_{out}) \quad (6)$$

where C_{in} and C_{out} represent inflow and outflow solute concentrations. Similarly the mean gradient or concentration difference across the membrane, which is the driving force for diffusion, is actually the log mean concentration gradient. When flow is countercurrent, the log mean gradient is:

$$[(Cb_{in} - Cd_{out}) - (Cb_{out} - Cd_{in})]/\ln[(Cb_{in} - Cd_{out})/(Cb_{out} - Cd_{in})] \quad (7)$$

where Cb depicts the blood concentration and Cd the dialysate concentration, and the subscripts in and out represent the dialyzer inflow and outflow. A rearrangement of Equation 2 shows that J, the solute flux (removal rate, e.g., in mg/min), can be expressed as the product of K_OA and the concentration gradient:

$$J = \text{Flux} = K_OA(\text{log mean gradient}) \quad (8)$$

Clearance (K_d), as defined for a device with flow, is the flux measured either on the blood side [Q_b (Cb_{in} - Cb_{out})] or on the dialysate side [Q_d (Cd_{in} - Cd_{out})] of the membrane divided by the inflow concentration:

$$\begin{aligned} K_d &= Q_b(Cb_{in} - Cb_{out})/(Cb_{in}) \\ &= -Q_d(Cb_{in} - Cb_{out})/(Cb_{in}) \end{aligned} \quad (9)$$

Combining Equations 3, 7, 8, and 9 yields a practical equation for calculating K_OA from an instantaneous measurement of solute clearance and both Q_b and Q_d when flow is countercurrent:

$$K_0A = \frac{Q_bQ_d}{Q_b - Q_d}\ln\left(\frac{Q_d(Q_b - K_d)}{Q_b(Q_d - K_d)}\right) \quad (10)$$

A rearrangement of Equation 10 gives another practical equation for calculating expected clearance from Q_b, Q_d, and K_OA. This equation eliminates the need to measure blood concentrations to predict the effect of changes in flow on clearance:

$$K_d = Q_b\left[\frac{e^{K_0A\left(\frac{Q_d - Q_b}{Q_dQ_b}\right)} - 1}{e^{K_0A\left(\frac{Q_d - Q_b}{Q_dQ_b}\right)} - \frac{Q_b}{Q_d}}\right] \quad (11)$$

Boundary Layers and Streaming Effects

Despite a rapid flow along the membrane, the solvent tends to adhere to the membrane creating a *boundary layer*, or unstirred layer, that adds to the diffusive pathway on both sides of the membrane.[110] This layer of solvent adjacent to the membrane tends to thin out as flow is increased or as turbulence is produced at the membrane surface. In addition to forming boundary layers, dialysate tends to move along the path of least resistance or channel, leading to nonuniform flow and bypassing some of the membrane area. This *streaming effect* is more pronounced at lower dialysate flow rates, especially in large dialyzers.[116] Both boundary layer and streaming effects cause K_OA (the resistance to solute diffusion across the membrane) to increase as dialysate flow increases,[117] although the effect is less in vivo than in vitro.[118,119] Recent changes in the shape of hollow fibers

and the insertion of inert spacer yarns have improved dialyzer performance further through reducing the effects of channeling and unstirred layers.[120,121] Both effects are less prominent on the blood side of hollow fibers because of the geometric advantages of flow within hollow fibers, the scrubbing effects of red blood cells, and less variance in Q_b.

High-Efficiency and High-Flux Dialyzers

Initial hemodialyzes were limited by low dialyzer membrane permeability, requiring more than 6 hours for each treatment. Although treatment times were shortened to 4 hours or less three times a week as dialyzer design improved, the time spent attached to the dialysis machine was still unacceptable to many patients. The next major advancement came in the late 1980s, when the technical problems with bacteriological contamination of bicarbonate dialysate, inadequate blood flow, imprecise ultrafiltration control, and continued low dialyzer solute clearance were solved.

The distinction between *high-efficiency* and *high-flux* dialyzers is not always made clear, and sometimes these terms are used interchangeably. In essence, both terms address improved solute and fluid clearance compared to standard hemodialyzers, taking advantage of higher blood and dialysate flow rates to decrease dialysis time while maintaining an adequate dose. The two dialyzer designs are not mutually exclusive and, in fact, frequently overlap (see Table 20-6). The high-efficiency dialyzer contains either a synthetic or a modified cellulose membrane and has a higher clearance of small molecules, such as urea (Table 20-6), compared to a standard dialyzer. The high-flux dialyzer always has a highly permeable synthetic or modified cellulose membrane that removes larger molecules. By their nature, high-flux dialyzers have a higher K_{Uf} compared to high-efficiency dialyzers but not necessarily high urea clearances (see Table 20-6). Conversely, high urea clearance defines high-efficiency dialysis, but the clearance of larger molecules is variable (see Table 20-6).

The advent of substituted cellulose and synthetic membranes improved dialyzer permeability because substituted cellulose membranes can be made thinner to increase porosity and surface area, whereas synthetic membranes can be manufactured with more and larger pores. Both high-efficiency and high-flux dialysis require the use of bicarbonate dialysate and volume-controlled filtration. Because the high-efficiency and high-flux dialyzers have a higher K_{Uf}, precise control of ultrafiltration is also mandatory to prevent massive volume depletion (see later Mechanics of Hemodialysis).

Because of their greater porosity, high-flux dialyzers can remove larger molecules.[112,113] Use of these membranes to improve β_2-microglobulin removal has been associated with a reduction in the risk of carpal tunnel syndrome in long-term patients treated with high-flux dialysis (see Chapters 13 and 24).[46,112,122,123] Other benefits that derive possibly from removal of large molecules are an improved lipid profile,[122,124,125] a greater response to erythropoietin,[126] a higher leptin removal (leptin is thought to suppress appetite),[127] and perhaps lower mortality and hospitalization rates.[122,123,128] Potential adverse consequences from increased removal of larger molecules, however, include greater removal of drugs such as vancomycin (see Chapter 15),[129] amino acids,[130] and albumin,[131] although the last-mentioned is disputed.[112] The presence of *back-filtration* during high-flux dialysis has been postulated to increase the risk of exposing patients to endotoxin from the dialysate, although this potential problem has not been clearly demonstrated in clinical studies.[132,133]

Only a few studies have evaluated the comparative efficacy of standard dialysis versus high efficiency and high flux. Nearly all high-flux dialyzers also have high efficiency, so most studies focus on high-flux versus standard hemodialysis. Randomized control or cross-over trials using bicarbonate dialysate found no difference in the incidence of hypotension and intradialysis symptoms[112,134] or in the control of blood pressure[135] among the three modalities. In a small number of patients treated with high-flux dialysis versus standard dialysis, neuropsychological function[136] was comparable. The best data available come from the HEMO Study, which detected no significant difference in mortality or morbidity between patients treated with standard versus high-flux dialysis and only a slight difference in subgroup analyses.[79] A more recent smaller study in Europe (MPO Study) found a small but significant improvement in mortality but only in the subgroup with low serum albumin levels (<4.0 g/dl).[137] These findings impact the toxic significance of middle and larger molecules (see later discussion).

HEMODIALYSIS

Using dialysis as a form of therapy for the patient vastly complicates this otherwise simple procedure. Factors that complicate the delivery of dialysis include the access device, the patient's compliance with the dialysis prescription and

TABLE 20-6 Characteristic Values for Standard, High-Efficiency, and High-Flux Dialyzers*

	STANDARD	HIGH-EFFICIENCY	HIGH-FLUX
Blood flow rate (ml/min)	250	≥350	≥350
Dialysate flow rate (ml/min)	500	≥700	≥700
K_OA urea	300-500	600-1000	Variable
Urea clearance (ml/min)	<200	250-400	Variable
Urea clearance/body weight (ml/min/kg)	<3	>3	Variable
Vitamin B_{12} clearance (ml/min)	30-60	Variable	>100
Ultrafiltration coefficient (ml/hr/mmHg)	3.5-5	<15	>15
Membrane	Cellulose	Variable	Variable

*See text.

diet, and solute disequilibrium. Developing standards of adequacy requires detailed studies of large populations, with careful attention to the multiple variables that, in addition to the dialysis itself, influence outcome. Achieving target solute concentrations in the patient during and between treatments requires complex mathematical models with multiple variables to account for differences among patients, including differences in size and solute generation rate. These factors add considerable complexity to the relatively simple laws of diffusion and flow discussed earlier, so that the solutions to patient problems are often approximations at best.

Types of Clearance

As noted in the discussion of dialysis and depicted in Equation 2, dialyzer clearance is the solute removal rate (flux) factored by the blood inflow concentration. During single-pass dialysis, the flux of urea is directly proportional to the inflow concentration, so that urea clearance tends to be constant despite the fall in blood concentration with time. The simplest type of clearance is the *instantaneous dialyzer clearance*, which can be measured by sampling blood on both sides of the dialyzer while recording Q_b at any instant in time. Although the dialyzer urea clearance tends to remain constant, it may fall during treatment because of loss of surface area from clotting or because of changes in Q_b or Q_d. The *effective clearance*, or *integrated dialyzer clearance*, accounts for these changes by linking the measurement of clearance to the predialysis and postdialysis blood urea nitrogen (BUN). This clearance is essentially the answer to this question: What average urea clearance would be required to drive the BUN down to the measured postdialysis value from the measured predialysis value?

The mathematical solution requires a process known as *urea modeling* (see Quantifying Dialysis). It can be calculated using either a single-compartment or a two-compartment urea kinetic model, entering a predialysis and immediate post dialysis BUN in the former case and multiple intradialysis and postdialysis BUN in the latter case. In either case, the result is a *dialyzer urea clearance* that is not affected by urea disequilibrium. The integrated dialyzer clearance is often called the *delivered clearance* to distinguish it from the *prescribed clearance*. The latter is simply the expected clearance derived from the dialyzer K_OA and flow rates (see Equation 11).

During dialysis, solutes must diffuse from body tissues into the blood to reach the dialyzer. Even within the dialyzer as blood passes through it, solutes must diffuse from within red cells to the plasma before diffusion can take place across the dialyzer membrane into the dialysate. The striking difference between the ability of urea and creatinine to traverse red cell membranes shown in Figure 20-9 explains in part why urea is preferred to creatinine as a marker for small solute clearance.[138] Such compartmentalization of body fluids adds complexity to the concept of clearance because different values may be chosen for the denominator of Equation 3. Even for urea, which diffuses easily across cell membranes from tissue to blood, some disequilibrium still develops among the various body compartments during dialysis as reflected in the postdialysis urea rebound shown in Figure 20-10. As a result, the patient's clearance, or *whole body clearance*, defined as the urea removal rate divided by the average urea concentration in total body water, is always less than the dialyzer clearance. Whole body clearance is a virtual clearance (not instantaneously measurable) that can be derived from single compartment modeling (see Mathematical Models) of the predialysis and *equilibrated* postdialysis BUN. Like dialyzer clearance, it is also a mean clearance integrated over time on dialysis, but it accounts for the presence of solute disequilibrium.

Adding further complexity to the concept of clearance are the frequency and duration of dialysis. Because *residual native kidney clearance* (K_r) exerts most of its effect between dialyses when dialyzer clearance is zero, it cannot be directly added to dialyzer clearance (see Quantifying Hemodialysis). *Intermittent clearance*, as obtained with hemodialysis, is inherently less efficient than the *continuous clearance* of native kidneys or continuous peritoneal dialysis. There are two explanations for this reduced *dialysis efficiency*.

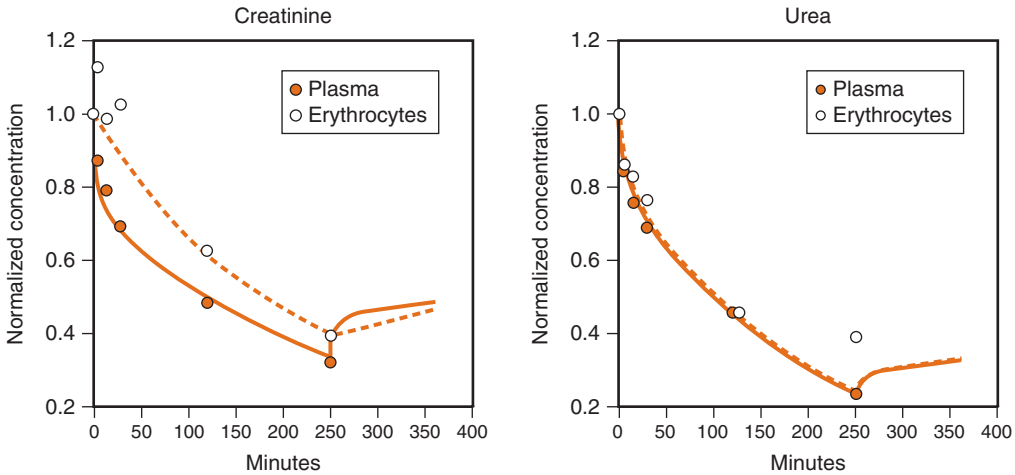


FIGURE 20-9 Disequilibrium within the dialyzer itself. Normalized concentrations predicted by a complex mathematical model are shown as solid (plasma) and dotted lines (erythrocyte); measured values are shown as solid (plasma) and open circles (erythrocyte). Urea is efficiently removed from erythrocytes within the dialyzer, but creatinine is not. (Adapted from D. Schneditz, D. Platzer, J.T. Daugirdas, A diffusion-adjusted regional blood flow model to predict solute kinetics during haemodialysis, Nephrol. Dial. Transplant. (2009) gfp023. Reprinted with permission of Oxford University Press.)

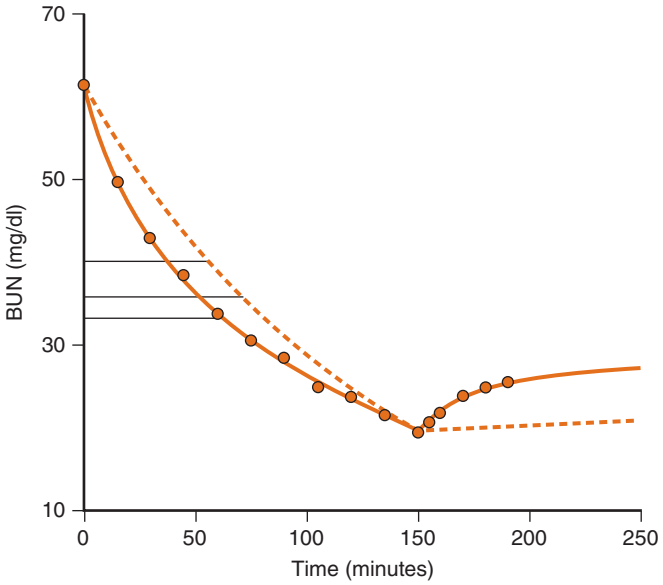


FIGURE 20-10 Changes in BUN concentrations during and after dialysis. Measured BUN levels during and immediately after dialysis fit best into a two-compartment variable-volume mathematical model *(solid line)*. The single-compartment variable-volume model *(dashed line)* overestimates BUN levels during the dialysis and fails to predict the rebound. The upper solid horizontal line at 40 mg/dl is the simple arithmetic mean of the predialysis and the postdialysis BUN. The middle solid horizontal line at 36 mg/dl represents the log mean BUN during the treatment, as predicted by the single-compartment model. The lower solid horizontal line at 34 mg/dl is the true mean BUN, obtained from actual measurements throughout dialysis.

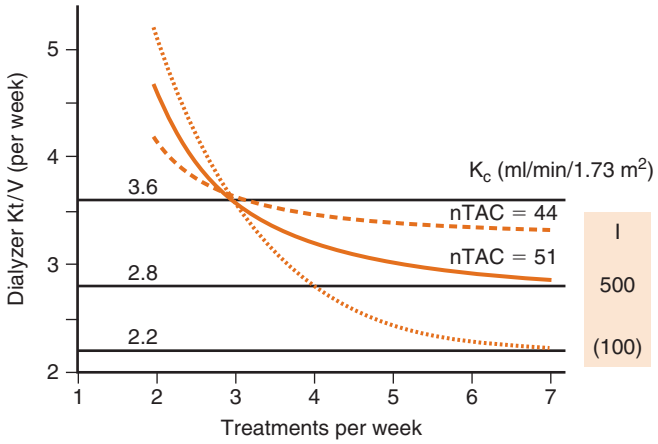


FIGURE 20-11 Urea kinetics value (Kt/V) required to maintain the same timed average urea concentration (TAC) of urea. To achieve the same mean BUN concentration, the dose of dialysis provided per week may be reduced as the frequency of dialysis increases. The upper solid line shows the required weekly Kt/V for urea based on an intercompartment mass transfer coefficient (K_C) of 500 ml/min. Even a simple single-compartment model with no resistance to diffusion in the patient (*dashed line* = infinite K_C) shows a dependence of weekly Kt/V on dialysis frequency. The discrepancy in weekly Kt/V between intermittent and continuous dialysis is even greater for a theoretical substance that dialyzes as well as urea but exhibits greater disequilibrium within the patient (*dotted line* = K_C of 100 ml/min). (Adapted from T.A. Depner, Quantifying hemodialysis and peritoneal dialysis: examination of the peak concentration hypothesis, Semin. Dial. 7 [1994] 315-317. Reprinted with permission of Blackwell Science, Inc.)

First, although dialyzer clearance is not compromised by an intermittent schedule, total solute removal is reduced because blood solute concentrations decline logarithmically and not linearly during dialysis (Figure 20-10).[80,111,139] Because solute levels do not change during continuous dialysis, this effect is absent, and solute removal is maximal at all times. Therefore, to reduce solute levels to a similar value, intermittent dialysis must be more intense when averaged over a week of treatment, as shown by the uppermost line in Figure 20-11. This explanation applies even in the absence of solute disequilibrium.

The second explanation applies to the more realistic situation in which solute concentration in the blood compartment is below that in other compartments as solute disequilibrium develops during dialysis. Here again dialyzer clearance is unaffected, but solute access to the dialyzer is limited (see later further discussion of Solute Disequilibrium). For continuous replacement modalities and native kidney function, the blood solute concentration is stable, and the effect of solute disequilibrium is minimal, so clearances are easy to calculate:

$$\text{(12)}\quad \text{Native kidney urea clearance} = K_r = (U_{urea} \times V)/(P_{urea} \times t)$$

$$\text{(13)}\quad \text{Peritoneal urea clearance} = (D_{urea} \times V)/(P_{urea} \times t)$$

where U_{urea} is urinary urea concentration, P_{urea} is blood urea concentration, D_{urea} is peritoneal dialysate urea concentration, t is time, and V is 24-hour urinary volume for Equation 12 and 24-hour dialysate volume for Equation 13.

Continuous clearances are easier to calculate but more difficult to measure than intermittent clearances. For hemodialysis, the clinician can take advantage of the dialysis-induced perturbations in urea concentrations to measure clearance and other patient variables that are not readily measurable by other means.

It is apparent from the previous discussion that the clearances measured during intermittent forms of dialysis are not directly comparable to native kidney clearance or clearances measured in patients undergoing continuous dialysis. The previous observations also help explain the significant difference between the minimum recommended weekly dose of dialysis (Kt/V) for hemodialysis (1.2 per dialysis × 3 dialyses per week = 3.6/week) and for peritoneal dialysis (1.8/week). To allow a direct comparison, the following formulas adjust for intermittence by calculating the continuous equivalent of intermittent clearance (equivalent Kt/V or EKR). For intermittent therapy during a steady state of urea nitrogen balance:[140]

$$\text{(14)}\quad EKR_{mean} = \frac{\text{removal rate}}{\text{mean concentration}} = \frac{\text{generation rate}}{\text{mean concentration}} = \frac{G}{TAC}$$

$$\text{(15)}\quad EKR_{peak} = \frac{\text{generation rate}}{\text{peak concentration}} = \frac{G}{\text{AV Peak BUN}}$$

G and TAC are derived from formal urea modeling. Using Equation 14 and adjusting for time and patient volume, the quantity of hemodialysis necessary to keep a patient's time-averaged BUN constant falls from a weekly Kt/V of 3.6 for

thrice weekly treatments to an EKR of 2.8 for continuous treatment.[141] If mean peak urea is substituted for TAC in Equation 15, the EKR falls to approximately 2, consistent with the current clinically accepted minimum adequacy for peritoneal dialysis (see Chapter 28).[142] Although the EKR_{peak} values defined by Gotch as "standard clearance"[142] better matches clinical experience, the argument that peak urea levels mediate uremic toxicity does not naturally follow because urea is relatively nontoxic. Instead the relationship likely reflects a fortuitous difference between the diffusibility of urea and the true uremic toxins.[80] One of the advantages of EKR is allowance of simple arithmetic addition of residual native kidney clearance to dialyzer clearance (see later text).

Quantifying Hemodialysis

Dialysis is a treatment born out of empiricism. Solute mass transport during dialysis has been described in precise mathematical terms but only after dialysis was established as a life-sustaining treatment for patients with advanced kidney failure. Much of the effort to describe the kinetics of solute transport has been devoted to determining how to best quantify the amount of dialysis prescribed and delivered. Because it is easy to measure and because the exact uremic toxin(s) are not known, mathematical models of urea kinetics have been used to quantify dialysis.

Mathematical Models of Urea Kinetics

Because urea is a highly water soluble molecule with little binding to proteins, it distributes in aqueous environments only. Its small size and lack of an electric charge in concert with specific pathways for membrane transport allow it to diffuse rapidly among the various body water compartments. The rate of diffusion is so rapid that a single space of distribution (total body water) can be assumed for most approximations. Between dialyses, when urea accumulates at a slow, constant rate and there is ample time for distribution among the compartments, this assumption is reasonable, and the single-pool, or *single-compartment kinetic model,* is appropriate. During dialysis, however, when blood concentrations change rapidly, urea gradients appear. Serum concentrations fall lower than predicted by the single-compartment model and rebound after dialysis, as shown in Figure 20-10. Because of this disequilibrium, more complicated mathematical models were developed to explain better the behavior of urea during dialysis.

The *two-compartment model* (Figure 20-12) assumes that the body is divided into two pools of water, with a finite resistance to diffusion between them. The resistance is expressed inversely as the intercompartment mass transfer coefficient (K_C), which is a measure of the average solute conductivity among compartments for the particular solute. K_C is analogous to K_OA, is solute specific, and has units of measurement that are similar to K_OA (ml/min). The mathematical solution in most cases suggests that the two compartments are the intracellular and extracellular pools separated by cell membranes, but the model does not require this assumption.

For solutes of larger molecular weight, varying charge, and bulkier configuration than urea, disequilibrium among the various compartments is even more pronounced, K_C is lower, and the solute gradients are even larger. Urea is unique in its ability to diffuse across cell membranes, especially the red cell membrane, where urea transporters have been found.[143,144] Most other solutes, even in the same range of molecular weight as urea, probably require a more complex kinetic model.

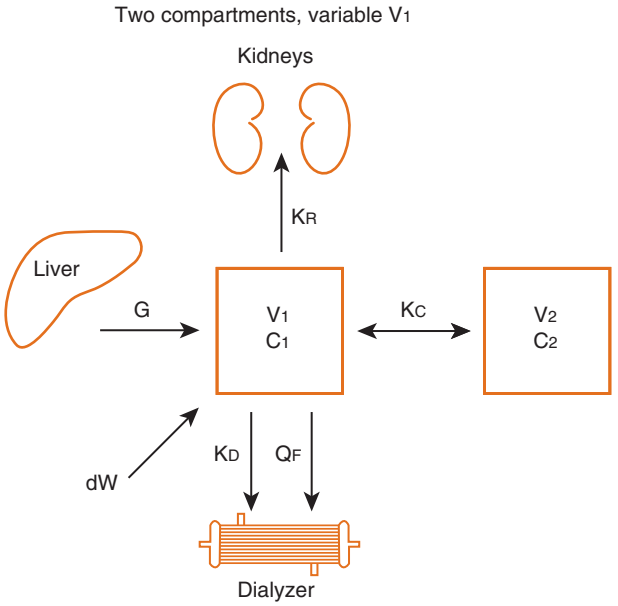


FIGURE 20-12 Two-compartment, variable (V)-volume (v) urea kinetic model. This model assumes that urea is distributed in two compartments (subscript 2). v and C are the volume and concentration of urea in each of the two compartments. *G,* urea generation rate; K_C, intercompartment mass transfer coefficient; K_R, residual native kidney clearance; K_D, dialyzer clearance; Q_F, rate of fluid removal during dialysis (From T.A. Depner, Prescribing Hemodialysis: A Guide to Urea Modeling, Kluwer Academic Publishers, Boston 1991.)

Kt/V_{urea}

The greatest lesson learned from the NCDS was that patient outcome correlates best with dialyzer urea clearance (K_d). When the level of any known solute is compared to urea clearance, the latter is better able to predict morbidity and mortality in dialysis populations.[145] To allow comparisons among patients and patient populations, a standard expression of clearance must be used, normalizing variables such as the frequency and duration of dialysis and patient size. Adjustment for size is most conveniently done using the patient's volume of urea distribution (V) as the denominator instead of the patient's surface area, commonly used for native kidney clearance. Standards for adequacy are currently available for hemodialysis delivered three times weekly. If K_d/V is multiplied by the duration of each dialysis (t), the result ($K_d \times t/V$) is a normalized or fractional clearance expressed per dialysis instead of per unit of time. During dialysis, total clearance is the sum of native kidney clearance and dialyzer clearance ($K_r + K_d = K$), so the fractional clearance per dialysis is more often expressed as Kt/V.

Equation 5 shows that simple first-order diffusion across a dialyzer membrane can be expressed as a constant fractional removal rate, if the dialysate concentration remains zero.

For hemodialysis with a constant blood flow and a constant single-pass flow of dialysate, fractional solute removal (dC/C) is also constant. Integration and log transformation of Equation 5 gives a powerful expression for the normalized clearance:

$$\text{Kt/V} = \ln(C_0/C) \quad (16)$$

Equation 16 shows that the normalized clearance (Kt/V) can be determined simply by measuring a predialysis BUN (C_0) and a postdialysis BUN (C). This eliminates the need to measure or estimate the dialyzer clearance, the native kidney clearance, the patient's urea volume, or even the duration of each dialysis to obtain this most powerful correlate to patient survival. It also provides an effective *delivered* clearance, because it is derived from measurements of the resulting change in BUN within the patient. Also basing the measurement of clearance on the concentration of urea instead of its removal rate automatically normalizes it to the patient's size expressed as V.

Equation 16 ignores urea generation during hemodialysis (G) and the change in volume that invariably occurs because of ultrafiltration (dV). These variables have significant effects on Kt/V (changing its value by up to 30%) that can be included in the expression if formal modeling is used to calculate Kt/V:

$$d(CV)/dt = G - (K/V)C \quad (17)$$

Equation 17 is a mathematical expression of single pool urea mass balance *described earlier*. Not only does its solution for the intradialysis interval give a more accurate measure of Kt/V, but also its *interdialysis* solution provides a method for calculating G and V and for expressing urea concentrations (C) at any specific time during the week:

$$C = C_0\left[\frac{V - B\cdot t}{V}\right]^{\left(\frac{K_r+K_d+B}{B}\right)} + \frac{G}{K_r+K_d+B}\left[1-\left[\frac{V-B\cdot t}{V}\right]^{\left(\frac{K_r+K_d+B}{B}\right)}\right] \quad (18)$$

where V is the solute distribution volume after dialysis (ml), and B is the rate of change in V (ml/min), which is usually negative during dialysis and positive between dialyses.

Residual Clearance

Because native kidney function is continuous and occurs between and during dialysis treatments, K_r cannot be simply added to K_d. To do so would grossly underestimate the contribution of K_r to overall excretory function. Two methods have been proposed to combine the two clearances to represent overall excretory function as a single clearance. The first inflates the continuous native kidney component to the equivalent of an intermittent clearance, in the form of Kt/V, before addition:[109]

$$\text{Kt/V}' = \text{Kt/V} + K_r \times 4500/V \quad (19)$$

Kt/V' is a new value for Kt/V and approximates the dialyzer clearance required to maintain the same solute levels and therefore the same risk to the patient. The second method is less widely used but is more exact. It essentially deflates the intermittent component to an equivalent continuous clearance:[140]

$$\text{EKR} = G/\text{TAC} \quad (20)$$

EKR is a combined clearance in ml/min that includes both the dialyzer and the residual clearance components expressed as a continuous clearance. It is calculated from the urea generation rate (G) and the mean BUN (TAC) obtained from formal urea kinetic modeling. Mathematical subtraction separates the two:

$$\text{EKR}_d = \text{EKR} - \text{Kr} \quad (21)$$

where EKR_d is the dialyzer component. This method does not take into consideration the greater efficiency of continuous native kidney clearance compared to intermittent dialyzer clearance as discussed previously. An attempt to include this factor led to the concept of "standard clearance" introduced by Gotch in 1998.[142] Although it represents a crude approximation, this concept was embraced by the K/DOQI committee on hemodialysis adequacy in their clinical practice recommendations.[34] The committee chose a conservative approach using a simplified method, but they emphasized the importance of measuring residual clearance both as a prognostic factor[146] and as a means of adjusting the dialysis dose. A conservative approach was taken because no studies have addressed outcome effects of adding dialyzer to native kidney clearance. HEMO Study participants were selected for lack of Kr, so one cannot extrapolate the lack of benefit in this study to patients with significant residual function. The risk from failure to adjust the dialyzer clearance in individual patients as Kr is lost also favors a conservative approach.

Dialysate Methods

The single-pool kinetic model discussed earlier estimates mass balance of urea across the dialyzer from changes in blood concentration. It makes several incorrect assumptions that cause the errors shown in Figure 20-10, but the two largest errors are in opposite directions and tend to offset one another.[111] This fortuitous balancing of errors has justified continued use of the single-compartment model to monitor dialysis adequacy. The indirect measurement of urea removal on the blood side, however, has been criticized by some who favor more direct measurements on the dialysate side to avoid these errors. However, use of instruments which measure dialysate urea concentrations either continuously (e.g., by urea electrode) or at multiple times intermittently[147,148] is important to ensure the accuracy of the dialysate method.[149] With these instruments, the dialysate curve-fitting method can be used, which is more accurate than the dialysate/volume method.[149] Dialysate monitoring offers additional advantages, including elimination of blood removal from the patient and avoidance of exposure to the patient's blood, eliminating this potential risk to the patients and staff.

Dialysate collection allows a more direct calculation of V from the amount of urea removed during dialysis divided by the change in concentration. Additional adjustments for ultrafiltration and urea generation yield:

$$V = \frac{Q_d C_d t_d - C_0 \Delta V - t_d(G - K_r C_{av})}{C_0 - C_e} \quad (22)$$

where t_d is the duration of dialysis, G is the urea generation rate, ΔV is the change in volume, K_r is the residual urea

clearance, C_d is the average dialysate urea concentration, C_{av} is the average serum urea concentration, C_0 is the predialysis BUN, and C_e is the equilibrated postdialysis BUN. Rearrangement of Equation 22 provides a method that avoids the delay required to measure directly the equilibrated postdialysis urea concentration:

$$C_e = \frac{C_0V - Q_dC_dt_d + C_0\Delta V + t_d(G - K_rC_{av})}{V} \quad (23)$$

eKt/V_{urea}

C_e obtained from Equation 23 can be used in place of the postdialysis urea concentration for calculating Kt/V using the single compartment model (spKt/V). This *equilibrated* value for Kt/V, or eKt/V is always lower than spKt/V but is more realistic because it avoids the rebound error that inflates the single pool value. eKt/V has been called the patient Kt/V because it reflects the actual change in BUN and removal of urea from the patient. A recent large population study showed that eKt/V can be predicted from spKt/V as a function of time on dialysis:[150]

$$\begin{aligned} eKt/V &= spKt/V - 0.6K/V + 0.03 \\ &= spKt/V(1 - 0.6/t) + 0.03 \end{aligned} \quad (24)$$

where K/V is spKt/V divided by t in hours. This estimate of eKt/V, when repeated in the same patient, had a lower variance than eKt/V measured using the dialysate method.[150,151] Although eKt/V is a more accurate measure of the dose actually received by the patient and was the target of the HEMO Study, it is not currently used as a yardstick of dialysis because there are no established standards with which to compare measured values.

Volume of Urea Distribution

The total body water volume is equal to the volume of urea distribution (V) and can be calculated using various methods, including indicator dilution,[111] bioimpedance,[152] or urea kinetic modeling.[111] V is most easily estimated from anthropometric formulas that are based on the patient's height (cm), weight (kg), sex, and age (years).[153–155] The most commonly used is the Watson formula:[153]

$$\begin{aligned} \text{Males}: V(\text{liters}) &= 2.447 - 0.09516 \times \text{age} + 0.1074 \times \text{height} \\ &\quad + 0.3362 \times \text{weight} \end{aligned} \quad (25)$$

$$\begin{aligned} \text{Females}: V(\text{liters}) &= -2.097 + 0.1069 \times \text{height} \\ &\quad + 0.2466 \times \text{weight} \end{aligned} \quad (26)$$

Equations 25 and 26 were designed to apply to all people with widely differing anatomy, but because V can vary independently of height and weight,[155] the anthropometric estimates of V have a large coefficient of variation.[153] V can be measured more precisely in individual patients by modeling urea kinetics because the model makes none of the assumptions found in the anthropometric formulas and because repeated modeling further reduces the variance. The resulting modeled V is analogous to V measured by indicator dilution methods, using urea as the indicator. The HEMO Study Group found that kinetically modeled V was consistently 13%–19% lower than that derived from the Watson equation.[156] It is unclear whether this difference indicates a reduction in total body water or a difference in the volume of water compared to the volume of urea distribution in patients with ESRD.

Urea Generation and Protein Catabolism

In anuric patients, serum urea concentrations reflect urea generation from net protein catabolism and removal of urea by dialysis. Virtually all urea derives from breakdown of amino acids, and conversely protein nitrogen is catabolized mostly to urea. Under steady-state conditions, only 10% of amino acid nitrogen is converted to nonurea nitrogenous wastes.[157,158] Furthermore, the net *protein catabolic rate* (PCR) approximates protein intake during a steady state of nitrogen balance. Therefore, the measurement of the *urea generation rate* (G), provided by formal urea modeling, allows an easy estimate of PCR and protein intake. In practice, PCR is usually normalized (divided) by V (PCRn) to allow comparison among patients of different size.

Based on independent detailed studies of two separate groups of patients, one group receiving dialysis[157] and the other with CKD not receiving dialysis,[158] the relationship between PCR (g/day) and G (mg/min) can be described with the following equation:

$$PCR = 9.35 \times G + 11 \quad (27)$$

Equation 27 shows that the majority of nitrogen released from excess catabolism of dietary and endogenous protein is converted to urea; only 11 grams of protein per day are converted to nonurea nitrogenous compounds, such as creatinine, uric acid, hippurate, and amino acids. The generation of nonurea nitrogenous compounds varies with patient size but not with daily protein intake, whereas the generation of urea depends upon protein intake. Adjusting the production of nonurea nitrogenous compounds for the average body size in these studies, using urea volume, and normalizing the entire expression to V,

$$PCRn = 5420\ (G/V) + 0.17 \quad (28)$$

where PCRn is normalized PCR in g/kg/day and V is the patient's urea volume (total body water) in liters.

The importance of PCR, PCRn, and G cannot be overemphasized. The NCDS showed that a consistently high BUN strongly predicted a poor outcome, but low BUN levels resulting from low urea generation rates (low PCRn) were associated with even higher morbidity and mortality.[159] A subsequent large population study[160] and the Modification of Diet in Renal Disease study (MDRD)[161] confirmed that patients with low protein intake and PCRn, and therefore low G, had high morbidity and mortality rates, possibly as a result of severe malnutrition, although other disease states may have suppressed the patients' appetites. These studies illustrate that it is not enough to know the BUN level; one must know how it got there. A low BUN from malnutrition is bad, but a low BUN from vigorous dialysis is good. Urea kinetic modeling allows the clinician to separate nutritional influences from the dialysis effect by examining both the absolute urea concentrations and the urea clearance derived from the fall in urea concentrations sampled immediately before and after dialysis.

The causes of low PCRn are myriad including inflammation, cardiovascular disease, and malignancy, often unrelated

to kidney failure or dialysis, and in most cases not responsive to increasing the dose of dialysis (Kt/V). In this regard, it is important to be aware of the spurious association in population studies between modeled Kt/V and PCRn as a result of error coupling. Because both measurements are derived from the same predialysis and postdialysis BUN, a spurious positive correlation occurs because of mathematical coupling of BUN measurement errors.[162,163]

Solute Disequilibrium

Solute disequilibrium is defined as a concentration difference or gradient for dissolved solutes among body compartments. This problem develops during dialysis and slowly dissipates over several minutes to hours after the end of dialysis (see Figure 20-10). Solute disequilibrium caused by resistance to diffusion across cell membranes is called *diffusion-dependent disequilibrium* (see Figure 20-12). When disequilibrium is caused by differences in blood flow among various vascular beds, it is termed *flow-dependent disequilibrium* (see Figure 20-13).

Older models of diffusion predicted that solute concentration differed among the various compartments but was uniform throughout the blood pool. More recent data suggest that solute disequilibrium among body compartments is at least partially caused by variances in tissue perfusion.[111,164–169] In fact, mathematical models have been developed that fully describe urea disequilibrium using purely flow-dependent disequilibrium.[167] These models assume that solutes diffuse instantly between compartments, so the observed gradients are attributed to differences in relative blood flow/volume served by the vascular bed. In reality, both mechanisms likely contribute but their relative importance remains to be determined.

Vascular access recirculation may cause a decrease in effective solute clearance[170–173] and is a special case of flow-dependent disequilibrium. Access recirculation occurs in about 5% of patients when blood that has just been dialyzed returns immediately to the dialyzer in the reverse direction through the access device. Multiple causes have been identified, including venous outflow stenosis, central venous stenosis, close proximity of the dialysis needles, and accidental reversal of the arterial and venous needles. Although dialyzer clearance is preserved, total solute removal decreases because the recirculated venous blood dilutes the solute concentration of the incoming arterial blood, thus lowering the solute concentration gradient across the dialyzer membrane. When 100% recirculation exists, all of the dialyzed blood returns to the dialyzer, and the patient derives no benefit from dialysis. Vascular access-related issues are addressed further in Chapter 21 and timing of the postdialysis blood sampling is discussed in Chapter 22.

With a model of *multiple parallel circuits*,[165] differences in blood flowing to various parts of the body have been invoked to explain the differences in solute concentration among these vascular beds during dialysis (Figure 20-13). Blood from the rapidly flowing circuits is exposed to the dialyzer more frequently and dilutes the solute concentration of blood flowing to the dialyzer. This essentially limits the access to the dialyzer of slower-flowing circuits that have higher solute concentrations. Thus differences in blood flow within the blood pool reduce the solute concentration

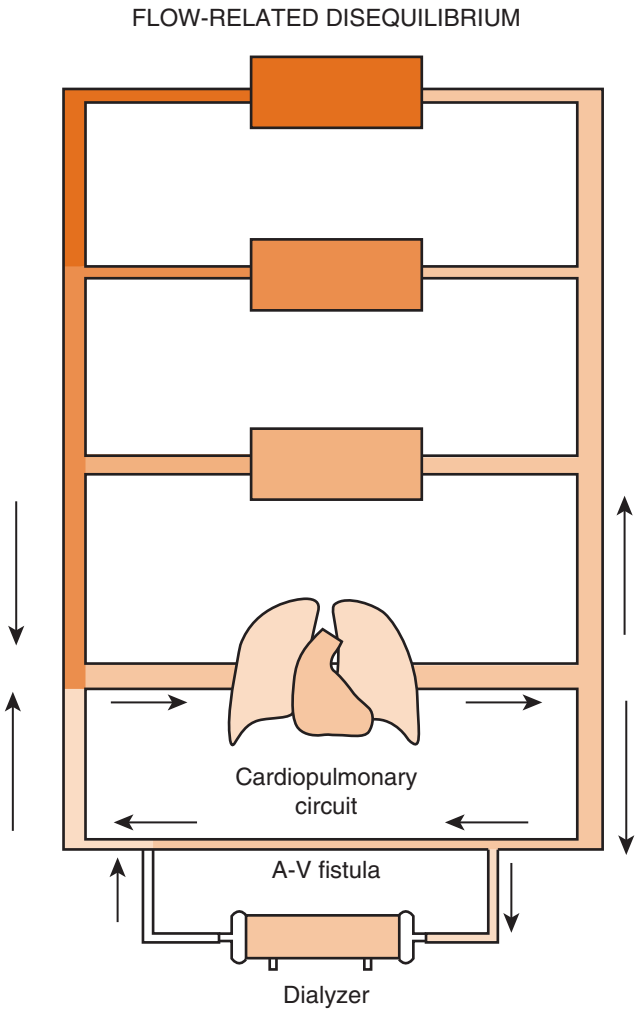


FIGURE 20-13 Urea disequilibrium as a consequence of differences in regional blood perfusion. Differing simultaneous concentrations of urea throughout the body can develop solely as a consequence of differences in regional blood perfusion, shown here as a parallel arrangement of tissue compartments. Although the consequences are similar to urea disequilibrium resulting from membrane-limited diffusion, the mechanism is entirely different because this model assumes an absence of diffusion barriers. Instead the rapid changes in blood urea levels at the beginning and end of treatment are caused by the differing blood perfusion rates. Blood in the more rapidly flowing circuits comes into contact more frequently with the dialyzer, so it has a lower urea and solute concentration and essentially dilutes the solute concentration from slower-flowing blood pools. The proximal and most rapidly flowing blood pathway is the cardiopulmonary circuit through the peripheral arteriovenous (AV) access device (From T.A. Depner, Approach to hemodialysis urea modeling, in: W.L. Henrich [Ed.], The Principles and Practice of Dialysis, fourth ed., Williams & Wilkins, Baltimore, 2009, pp. 73-96.)

entering the dialyzer and the average concentration in the patient. This reduces the efficiency of dialysis, decreases solute removal, and invalidates the use of solute concentration in peripheral venous blood for calculating vascular access recirculation.[165,166,169]

"Cardiopulmonary recirculation", present in dialysis patients with AV shunts (see Figure 20-13),[168] is a specific example of one of these multiple parallel circuits. Because the vascular shunt has low resistance and routes blood directly from the arterial to the venous circulation, blood flowing through this circuit returns to the heart at a faster

rate. Although the dialyzer clearance is unaffected, the concentration gradient across the dialyzer membrane is reduced by cardiopulmonary recirculation so that solute removal is impaired. Cardiopulmonary recirculation contributes to the rebound in blood solute (urea) concentration after dialysis is completed, as the various blood compartments equilibrate. Cardiopulmonary recirculation is not present in patients with central venous catheters for vascular access because blood drawn from the central vein is returned to the same vein, and the shunt circuit is absent.

Body Size and Dialysis Adequacy

Current standards factor the dose of hemodialysis according the patient's urea volume (V), which is equated to total body water volume. This is a departure from the usual body surface area (BSA) denominator but has the tremendous advantage of convenience, as outlined previously. Use of V is also logical if the goal is to maintain concentrations equal among different sized patients. This logic, however, depends not on V but on toxin generation rates that are proportional to V. Although we have little understanding of toxins, as discussed previously, it is likely that generation rates, much like other physiological functions, correlate more closely to BSA than V. Variability in the slope of outcomes related to dose also suggest that another denominator would be more appropriate, especially in population studies.[174] Clinical concerns include the potential for underdosing small patients and women.[175,176] This issue has been subject to scrutiny and methods for converting the denominator have been proposed but are not yet a standard of care.[177,178]

Adequacy of Hemodialysis: Current Recommendations

Before the NCDS, absolute blood urea concentrations were used to monitor the efficacy of dialysis and to determine the frequency of dialysis. Kinetic modeling gained popularity and increasing acceptance after the NCDS reported that both high and low blood urea concentrations were associated with increased mortality,[145,159] highlighting the fact that the absolute blood urea concentration is a poor marker of uremia and dialysis dose. Using absolute blood urea levels risks setting in motion the vicious cycle of providing less dialysis to patients who are malnourished, causing a further reduction in BUN. Assessing dialysis adequacy with kinetic modeling avoids this vicious cycle because kinetic modeling determines the clearance of urea, based on the *change* in urea concentration.

The NCDS data showed that maximal benefit from dialysis was obtained above a Kt/V_{urea} of 1 per dialysis administered three times a week.[159] Subsequent data from uncontrolled studies suggested that further benefit may be derived from increasing Kt/V_{urea} to 1.2 or greater (see Chapter 22).[91–94] Based on the available data, the NIH, the Renal Physicians Association, and the National Kidney Foundation (NKF) established the minimum Kt/V_{urea} at 1.2 per dialysis administered three times a week in their respective consensus conferences. The HEMO Study results support this minimum Kt/V_{urea} because increasing single pool Kt/V_{urea} from an average of 1.32 to 1.71 did not further reduce mortality or morbidity.[79] The NKF additionally recommended the application of formal urea kinetic modeling (see Quantifying Hemodialysis) for routine quantification of hemodialysis.[34] If formal modeling is not available, simplified formulas should be used.

Filtration and Dialysis

Because fluid nearly always accumulates in patients between therapeutic hemodialyses, net ultrafiltration must be a part of each treatment to maintain fluid balance. In a sense, water is also a toxin that accumulates and must be removed on a regular basis. The mechanism of water removal during hemodialysis is not diffusion but pressure filtration of the blood as it passes through the dialyzer. Although filtration also removes solute, and solute removal by filtration is also a first-order process, the additional clearance from filtration is often less than expected. Conversely, one can remove solute with filtration alone (see later Hemofiltration and Hemodiafiltration Therapy). If no dialysis takes place and the sieving coefficient is close to 1, the clearance is simply the filtration rate (see later Quantitative Contribution of Filtration to Solute Removal). The sieving coefficient is the fractional concentration of the solute in dialysate compared to blood water.

Often patients and sometimes the technical staff equate removal of fluid to the effectiveness of a dialysis session because fluid removal is visibly measurable. Of course, if therapeutic dialysis removed only fluid, the patient would quickly die of uremia. Removal of toxic solute by diffusion, the most significant goal of dialysis, is a silent process, detectable only by measuring solute levels in blood or dialysate samples; removal of fluid is easily displayed by modern volume-controlled dialysate delivery systems and is evident from the change in patient weight.

Dialyzer Ultrafiltration Coefficient

The same membrane properties (i.e., thinner, more porous membranes with a large surface area) that improve solute clearance also improve hydraulic fluid removal. In addition, membrane tensile strength plays a role in determining the maximum pressure that can be applied. Dialyzers are rated by their *ultrafiltration coefficient* (K_{Uf}), with units of ml/hr/mm Hg. Typical K_{Uf} values for standard and high flux dialyzers are listed in Table 20-6.

Quantitative Contribution of Filtration to Solute Removal

As plasma water moves from the blood compartment to the dialysate, solutes dissolved in plasma follow passively. Convective clearance thus augments diffusive transport, and the contribution can be quantified mathematically. When ultrafiltration is present during dialysis, blood flow into the dialyzer (Q_{bi}) can be expressed as the sum of blood flow out of the dialyzer (Q_{bo}) and the ultrafiltration rate (Q_f):

$$Q_{bi} = Q_{bo} + Q_f \quad (29)$$

From the previously described definition of dialyzer clearance and considering mass balance, dialyzer clearance (K_d) can be expressed as a function of solute concentrations and blood flow rates through the dialyzer:

(30) $K_d = J/C_{in} = [(C_{in} \times Q_{bi}) - (C_o \times Q_{bo})]/C_{in}$

where J is the solute flux, C_{in} the inlet (arterial) solute concentration, and C_o the outlet (venous) solute concentration. Combining and rearranging Equations 29 and 30 yields the following:

(31) $K_d = Q_{bi}(C_{in} - C_o)/C_{in} + Q_f(C_o/C_{in})$

Equation 31 shows that dialyzer clearance of a particular solute is the sum of solute clearance in the absence of ultrafiltration ($Q_{bi} = Q_{bo}$) and a fraction of the ultrafiltration rate. At one extreme, when all the solute is removed by diffusion ($C_o = 0$), there is no contribution from ultrafiltration. At the other extreme, when no diffusion is present ($C_{in} = C_o$), the dialyzer clearance is the ultrafiltration rate. This latter case occurs in the setting of hemofiltration (to be discussed further), where all solute clearance results from filtration. During the usual hemodialysis treatment, the contribution of convective clearance to the total dialyzer clearance is small. Even at high rates of ultrafiltration (2 L/hr or 33 ml/min), the relative contribution of ultrafiltration to total urea clearance is only about 10 ml/min or 5%, assuming C_o/C_{in} for urea of 0.3 to 0.4 and dialyzer urea clearance of 200 ml/min.

In clinical practice, outlet solute concentration is rarely measured, limiting the usefulness of Equation 31. With further mathematical manipulation,[111] C_o can be eliminated, yielding:

(32) $K_d = K_{d0} + Q_f(1 - K_{d0}/Q_{bi})$

where K_{d0} is the dialyzer clearance without ultrafiltration and can be calculated from Q_{bi} and the dialyzer K_OA. Q_f is readily calculated from the weight loss during dialysis divided by the duration of dialysis or directly measured by volume-controlled dialysis machines.

Hemofiltration and Hemodiafiltration Therapy

Up to now, we have discussed the principles of filtration in the context of hemodialysis, using filtration mainly for removing excess fluid, while relying on diffusion for solute removal. *Hemofiltration* alone can also be used to remove both solute and solvent. As discussed earlier and as evident from Equation 32, in the absence of diffusion ($K_{d0} = 0$), dialyzer clearance is the ultrafiltration rate. Therefore, to achieve solute clearance comparable to that of hemodialysis, large amounts of fluid must be removed, on the order of 30 to 80 L during each treatment, with simultaneous replenishment using a pyrogen-free physiological salt solution.[179,180]

Larger-molecular substances are removed more effectively by hemofiltration because convection has a greater effect of enhancing the relatively slow diffusive movement of larger molecules compared to small molecules (see earlier discussion of convection and diffusion). Hemofiltration requires a highly permeable (high-flux) membrane to achieve the high filtration rates (30 to 80 L per dialysis). During filtration, peripheral vascular resistance has been observed to increase in part due to a cooling effect,[181] which helps support the blood pressure. The primary disadvantage of hemofiltration is the large amount of sterile replacement fluid required, but equipment designed to simplify hemofiltration and produce sterile replacement fluid on-line is available in some countries.[180,182]

Hemodiafiltration is the combination of hemodialysis and hemofiltration (i.e., addition of dialysate flow to the hemofiltration circuit). Solute removal is accomplished by both diffusion and filtration, but, in contrast to traditional hemodialysis, the filtration component contributes much more because of its higher magnitude relative to dialysis. Although intermittent hemofiltration and hemodiafiltration are not widely used in the United States for treating ESRD, these two modalities have been adapted for wide use in intensive care units to treat patients with acute kidney failure.[183,184] Outcome benefits of hemofiltration and hemodiafiltration in comparison to hemodialysis have not been clearly established. Some small studies have suggested a comparative benefit[185] but in aggregate, current data do not justify one modality over the other.[186]

Filtration Effects on Blood Pressure, Regional Blood Flow, and Solute Removal

Blood pressure falls as fluid is removed (see Chapter 24), in part, because the normal response of vasoconstriction to fluid removal is impaired in dialysis patients. Use of bioincompatible membranes and acetate as a source of bicarbonate during hemodialysis can cause vasodilation and further predispose the patient to hypotension. To aggravate the situation further, solute removal decreases blood osmolarity, causing slight fluid shifts from the intravascular compartment into the intracellular compartment. In patients at high risk of hypotension during dialysis, separating filtration *(isolated ultrafiltration)* from dialysis may improve their hemodynamic stability.

Although theoretically filtration may account for a significant fraction of solute removal during hemodialysis, in practice it can also interfere with solute removal by diffusion. In addition, the development of intravascular volume depletion during dialysis causes vasoconstriction in the skin and skeletal muscle and shunts blood through more central vascular circuits (such as the AV shunt), enhancing flow-related solute disequilibrium.

Middle and Large Molecule Removal

Middle molecules (MM) were originally defined by Scribner and his associates as poorly dialyzable solutes that might account for the failure of more intense dialysis to restore health.[187] They imagined that these solutes were "membrane restricted" meaning that their clearances were limited by membrane porosity and surface area independent of blood and dialysate flow rates (Figure 20-14). An increase in MM clearance requires larger and more porous membranes or an increase in treatment time. These theoretical solutes were considered to be dialyzable by the membranes available at the time, but clearances were low. Because the available cellulosic membranes had an effective size cutoff of 10 kDaltons, the molecular weights of MMs were postulated to range from 500 to 3000 Daltons. More recent investigators have attempted to redefine the upper MM size limit to the 20,000–30,000 Dalton range to accommodate the greater porosity of modern high-flux dialyzers.[42] However, it is important to recall that anuric patients treated with these

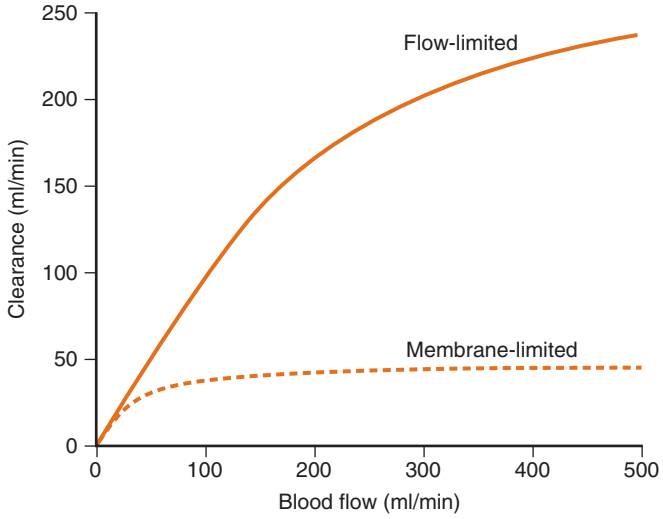


FIGURE 20-14 **Clearance of Small and Large Solutes.** Clearance of larger solutes tends to be membrane-limited, as depicted in the lower curve, unaffected by changes in blood or dialysate flow within the usual therapeutic range. For the smaller more diffusible solutes like urea, an increase in blood flow causes a near-proportionate increase in clearance within the therapeutic range of blood flow.

older cellulosic dialyzers survived, sometimes for more than a decade. This observation diminishes but does not eliminate the potential impact of MMs on survival or quality of life.

The middle molecule theory was popular in the 1960s and 70s, spurred by the failure of biochemists to identify specific uremic toxins in the low molecular weight range. Many thought that small polypeptides accounted for the uremic syndrome and encouraged membrane manufacturers to improve MM removal by developing high-flux dialyzers. Biochemists were similarly encouraged to look for toxic polypeptides that depended on renal elimination and that were retained in ESRD.[188,189] Polypeptides in the 500 to 3000 Dalton range are not abundant in the urine but are nonetheless dependent on kidney function for elimination by filtration and destructive reabsorption. The popularity of the MM theory at the time of the design phase of the NCDS likely had an influence on the decision to include dialysis treatment time as one of the two interventions because high-flux membranes were not yet available. The hypothesis tested by the NCDS was that retention of low molecular weight solutes, reflected in urea TAC, was more important than retention of MM's, the surrogate for which was treatment time. Because the results overwhelmingly favored TAC as the primary determinant of outcome, the popularity of the MM hypothesis diminished, and more emphasis was subsequently placed on improving small molecule clearances in the form of Kt/V_{urea}.[145] The quest for middle and larger molecular weight toxins is still ongoing, but the rationale has shifted to their potential contribution to the residual syndrome.

Importance of Treatment Time

In the early 1990s emphasis was placed on shortening the treatment time while maintaining an "adequate" Kt/V. It soon became apparent, however, that the effective clearance was treatment time-dependent (see previous discussion of eKt/V and equation 24),[80,190,191] and that outcomes were adversely affected by shortening dialysis time.[192,193] Shortening the treatment time will predictably decrease efficiency because it accentuates the effects of intermittence and exacerbates solute disequilibrium (see Solute Disequilibrium and Figure 20-10). In addition, as discussed earlier, the shorter duration of high-efficiency hemodialysis may not allow sufficient time to remove larger molecules, such as β_2-microglobulin, for which removal is more time-dependent.[112,113,194] Advocates of longer treatment times pointed to the more prolonged treatments in Europe and Japan, where outcomes are better than in the United States, and to the borderline significant effect of treatment time in the NCDS.[195] Another potential problem with shortening time is the required increase in the filtration rate.[112,134,196] Most patients can tolerate up to 0.35 ml/min/kg of filtration (1.5 L/hr in a 70-kg person) without developing nausea, cramping, or hypotension.[196] Therefore, an average-sized patient whose weight gain exceeds 4 to 5 kg is a poor candidate for short-duration dialysis and will experience a progressive rise in end-dialysis weight, eventually leading to pulmonary edema. Finally, once patients are accustomed to the shorter time, they are devastated psychologically when their medical condition, such as large fluid gains, inadequate clearance of larger molecules, poorly functioning access, or loss of residual kidney function, requires prolonging dialysis time. More recently the K/DOQI committee has recommended treatment times no shorter than 3 hours when given 3 times a week in anuric patients regardless of body size.[34]

MECHANICS OF HEMODIALYSIS

Twenty to 30 years ago, hemodialysis equipment for a single patient occupied the greater part of an entire room. Now hemodialysis machines are about the size of a 3- to 4-drawer filing cabinet and can be transported easily by one person. In addition to the reduction in size, advances have included more reliable dialysate delivery systems, monitoring devices, and automated safety mechanisms. Several on-line devices allow dynamic monitoring of the vascular access, the hematocrit, and the adequacy of the treatment.

Dialysate Delivery Systems

The most commonly used system discards the dialysate after a single passage through the dialyzer (*single-pass* delivery). Most dialysis clinics also use *single-patient* delivery systems in which a machine at each patient station continuously prepares dialysate by mixing a liquid concentrate with a proportionate volume of purified water. To dilute the concentrates safely, the dialysis machine has many built-in safety monitors. Some clinics use a central multipatient delivery system in which either the concentrated dialysate is mixed in an area away from patient care and then piped to each dialysis station, or the concentrate is piped to each station before mixing. The advantages of these centralized systems are lower patient care costs and less staff back injuries from carrying the individual concentrate jugs, but a major disadvantage is

inflexibility in modifying the dialysate concentration of electrolytes, such as calcium and potassium, to suit individual patient needs.

Mechanical and Safety Monitors

The dialysis machine draws up and warms purified water to physiological temperatures. The heated water then undergoes *deaeration* under vacuum to prevent dissolved air from coming out of solution as negative pressure is applied during dialysis. Air bubbles in the dialysate cause the blood leak detector and the conductivity detector to malfunction. They also "lock" part of the dialysate pathway, increasing channeling and masking parts of the membrane surface area.

The heated and deaerated product water is then mixed with the concentrate to produce dialysate. To ensure proper proportioning, the *conductivity monitor* downstream from the proportioning pump continuously measures the electrical conductivity of the product solution. Because malproportioned dialysate may cause severe electrolyte disturbances in the patient, leading to death, the conductivity monitor has a narrow range of tolerance and is usually redundant. Dialysate conductivity may be altered by temperature, the presence of air bubbles, or malfunction of the sensor, usually an electrode. Periodically, the conductivity monitor must be calibrated using standardized solutions or by laboratory measurements of electrolytes in the dialysate.

Because the patient is exposed to 100 to 200 L of dialysate during each treatment, the dialysate must be heated to near body temperature to avoid hypothermia. If the dialysate is too hot, however, protein denaturation (>42°C) and hemolysis (>45°C) occur. In practice, the dialysate temperature is maintained at 36° to 37°C and falls slightly in transit from the proportioning device to the patient. The *temperature monitor* within the dialysate circuit sets off an alarm if the dialysate temperature is outside of the limits of 36° to 42°C, and dialysate is pumped directly to the drain, automatically bypassing the dialyzer.

Located downstream from the dialyzer, the *dialysate pump* controls dialysate flow and generates negative dialysate pressure. The dialysate circuit must be able to generate both negative and positive dialysate pressures within the dialyzer because, although many dialyzers require a negative dialysate pressure for filtration, dialyzers with high K_{Uf} or conditions that increase pressure in the blood compartment require a positive dialysate pressure to limit filtration. The dialysate circuitry controls the pressure by variably constricting the dialysate outflow tubing while maintaining a constant flow rate. The dialysate delivery system also monitors the filtration rate, either indirectly by controlling the TMP (*pressure-controlled* ultrafiltration) or directly by controlling the actual filtration (*volume-controlled* ultrafiltration). Earlier dialysate delivery systems used pressure-controlled filtration, requiring dialysis personnel to calculate the TMP, enter the TMP into the machine, closely monitor the filtration rate, and recalculate and adjust the TMP as needed. To prevent excessive fluid removal when using dialyzers with K_{Uf} greater than 6 ml/hr/mm Hg, dialysate delivery systems capable of performing volume-controlled filtration are mandatory. Such systems have built-in balance chambers and servomechanisms that accurately control the volume of fluid removed during dialysis once the desired goal is set.[197]

The *blood leak monitor* is situated in the dialysate outflow tubing and is designed to alarm and shut off the blood pump when blood is detected. The presence of blood in the dialysate usually indicates membrane rupture and may be caused by a TMP exceeding 500 mm Hg. Although a rare complication, membrane rupture can be potentially life-threatening because it allows nonsterile dialysate to come into contact with blood. In this era of dialyzer reuse, the potential for membrane rupture is increased because both bleach and heat disinfection can damage the dialyzer membrane (see Chapter 24). Intravascular hemolysis with hemoglobin in the dialysate may also trigger the blood leak alarm.

Bicarbonate Delivery

Previously dialysate contained acetate as a source of bicarbonate. Advantages of acetate included the low incidence of bacterial contamination, no precipitation with calcium, and its ease of storage. However, acetate is a hemodynamic stressor especially during high-efficiency and high-flux dialysis[198,200] (see Chapters 22 and 24) when the rate of acetate diffusion into blood can exceed the metabolic capacity of the liver and skeletal muscle. Acetate accumulation leads to acidosis, vasodilation, and hypotension. All clinics using high-flux dialysis and the majority using standard flux dialysis now use bicarbonate-based dialysate to prevent these complications.

The major complications of bicarbonate dialysate are bacterial contamination and precipitation of calcium and magnesium salts. Gram-negative halophilic rods require sodium chloride or sodium bicarbonate to grow and thus thrive in bicarbonate dialysate.[201,202] When bicarbonate containers are disinfected, these bacteria have a latency period of 3 to 5 days, have an exponential growth phase at 5 to 8 days, and achieve maximum growth at 10 days,[201] compared to a latency of 1 day, exponential growth phase at 2 to 3 days, and maximum growth by 4 days in a contaminated container. Mixing bicarbonate and disinfecting the containers daily help prevent bacterial contamination. Alternatively, commercially available dry powder cartridges can circumvent this problem. Recognition of the risks from microbiological contamination and the subsequent steps taken to prevent contamination have greatly reduced the incidence of pyrogen reactions reported during the early application of high-flux dialysis. Although the risk is theoretically increased by back filtration during high-flux dialysis, few reports of this complication have appeared.[132,203]

To prevent formation of insoluble calcium and magnesium salts with bicarbonate, the final dialysate is mixed from two separate components: the bicarbonate concentrate and the acid concentrate. The acid concentrate contains all solutes other than bicarbonate and derives its name from the inclusion of a small amount of acetic acid (4 mEq/L in the final dilution). The dialysate delivery system draws up the two components separately and mixes them proportionately with purified water to form the final dialysate. This process minimizes but does not eliminate the precipitation of calcium and magnesium salts, so the dialysate delivery system must be rinsed periodically with an acid solution to eliminate any buildup.

Water Quality

Treatment of the water used to generate dialysate is essential to avoid exposure during dialysis to harmful substances, such as aluminum, chloramine-T, endotoxin, and bacteria. Accumulation of aluminum in the body may cause dialysis dementia, microcytic anemia, and osteomalacia. Chloramine-T, a product of chlorine and organic material, causes acute hemolysis during dialysis. Endotoxin and bacteria cause febrile reactions and hypotension. Good water quality is even more imperative when dialyzers are reused because the blood compartment is exposed to unsterile water and any accompanying bacteria or endotoxin. To avoid these complications, tap water is first softened, then exposed to charcoal to remove contaminants such as chloramine, then filtered to remove particulate matter, and then filtered under high pressure (reverse osmosis) to remove other dissolved contaminants (see Chapter 24).

Blood Circuit Components

The steady flow of blood required for dialysis may be drawn from a central vein, from the ports along the sides of a double-lumen catheter (arterial lumen), and returned through the port at the distal tip (venous lumen). Alternatively, the blood may be drawn from an AV fistula or graft through an "arterial" needle and returned through a second "venous" needle. The blood pump is usually a peristaltic roller pump, which sequentially compresses the pump segment of the blood tubing against a curved rigid track, forcing blood from the tubing. After the roller has passed, the elastic tubing recoils and refills with blood, ready for the next roller. As a result, blood flow through the dialyzer is pulsatile. Most pumps have two or three rollers. The greater the number of rollers, the less pulsatile the flow, but the higher the risk of hemolysis and damage to the pump segment.

Alternatively, the dialysate delivery system can be configured with one blood pump and two pressure-controlled blood-line clamps or two pressure-controlled blood pumps that will allow the delivery of dialysis through a single-needle in the vascular access or a single-lumen catheter.[204,205] This configuration offers less trauma to the vascular access but suffers from an increase in recirculation and hemolysis[205] and potentially a decline in adequacy, although this is debated.[204–206]

When the upper or lower limits are exceeded, *pressure monitors* sound an alarm and turn off the blood pump. An arterial pressure monitor should be located proximal to the blood pump and a venous monitor located distal to the dialyzer. Accepted ranges for arterial inflow pressures are −20 to −80 mmHg, but may be as low as −200 mmHg when Q_b is high. Accepted ranges for venous pressures are +50 to +200 mmHg. Kinks in the tubing, improper arterial needle position, hypotension, or arterial inflow stenosis can cause excessively low arterial pressures. High venous pressures should prompt an investigation for blood clotting in the dialyzer, kinking or clotting in the venous blood lines, improperly positioned venous needles, infiltration of a venous needle, or venous outflow stenosis. Accurate measurements of both the arterial and venous pressures are essential to determining the TMP. Excessive positive pressures anywhere in the blood compartment may rupture the dialyzer membrane or cause the blood circuit to disconnect. An abrupt fall in pressure anywhere in the blood circuit may signal an accidental disconnection of the blood circuit, which can result in exsanguination if not corrected promptly.

Two other important safety devices, located in the blood line distal to the dialyzer, are 1) the *venous air trap* and 2) the *air detector*. The venous air trap prevents any air that may have entered the blood circuit through loose connections, improper arterial needle position, or the saline infusion line from returning to the patient. If air is still detected in the venous line after the venous air trap, the machine alarms and turns off the blood pump. Excessive foaming of blood will also trigger the air detector. These safety features prevent air embolism, which carries a high mortality rate, especially when the problem is not immediately recognized.[207]

Computer Controls

As discussed earlier, solute removal during hemodialysis decreases plasma osmolarity, favors fluid shift into the cells, and makes fluid removal more difficult. Increasing the dialysate sodium concentration helps to preserve plasma osmolarity and allows continued fluid removal,[208,209] but may lead to increased thirst, excessive weight gain, and hypertension (see Chapter 24).[208,210] Computer-controlled sodium modeling allows the dialysate sodium concentration to change automatically during dialysis according to a preselected profile, usually 150 to 160 mEq/L at the beginning of dialysis to 135 to 140 mEq/L near or at the end of dialysis. Theoretically, this sodium modeling offers the benefit of greater hemodynamic stability while minimizing thirst and interdialysis hypertension. To date, a few small studies support this theory,[210–214] but the results are not conclusive.[215,216] Most authorities advise against sodium modeling.[34]

Ultrafiltration modeling, like sodium modeling, provides a variable rate of fluid removal during dialysis, according to a preprogrammed profile (linear decline, stepwise changes, or exponential decline of filtration rate with time). Altering the filtration rate during dialysis theoretically allows time for the blood compartment to refill from the interstitial compartment, leading to improved hemodynamic stability and less cramping. As with sodium modeling, ultrafiltration modeling must be individualized. In fact, the effects of the two are difficult to distinguish because they are often used together.[211,214,215,217]

Recent technological advances include the development of dialysis machines with *feedback control systems* that allows for computer-controlled adjustments of the ultrafiltration rate and dialysate conductivity to prevent the blood volume from dropping below a preset value throughout the dialysis session.[218,219] Studies in small groups of hemodialysis patients have demonstrated that this device reduces symptoms in both hypotension and nonhypotension prone patients.[218,220,221] The ability to monitor plasma conductivity throughout dialysis also ensures sodium balance during treatment, despite constant modifications to the dialysate conductivity and may reduce the problem of thirst and interdialytic hypertension

observed with sodium modeling.[218] Automated control of dialysate temperature to maintain isothermic dialysis (constant body temperature) was superior to thermoneutral dialysis (using lower but constant dialysate temperature) in reducing intradialytic hypotension.[218,222]

Anticoagulation

Blood clotting during dialysis is a source of patient blood loss and interferes with solute clearance by decreasing the dialyzer surface area.[223] To prevent clotting, a dose of heparin, the most commonly used anticoagulant in dialysis, is usually given at the start of dialysis (2000-5000 units or 50 units/kg), then continuously infused (1000-1500 units/hr) into the blood circuit before the dialyzer, until 15-60 minutes before the end of dialysis.[224–226] Alternatively, heparin boluses may be given intermittently during dialysis as needed. The bolus method increases nursing time and results in episodes of over anticoagulation and under-anticoagulation. If the patient is at risk of bleeding, low-dose heparin (bolus of 500 to 1000 units followed by 500 to 750 units/hr) or no anticoagulant may be appropriate.[225,226] For heparin-free dialysis, prerinsing the blood circuit with heparinized saline and flushing the dialyzer with 100 ml of 0.9% sodium chloride every 15 to 30 minutes may help to prevent clotting. Avoiding blood or platelet transfusions through the circuit is also required to minimize clotting. Additional options are the use of heparin-coated dialyzers or regional citrate anticoagulation,[226–228] although heparin-coated dialyzers may be inferior to regional citrate anticoagulation in preventing dialyzer clotting.[227]

Alternatives to heparin and regional citrate anticoagulation include low-molecular-weight heparin,[226,229–231] hirudin,[226,232] prostacyclin,[233,234] dermatan sulfate,[226] and argatroban.[235,236] Except for low-molecular-weight heparin, which is becoming standard in Europe,[226,231] none is in wide use because of complexity, expense, lack of sufficient clinical experience, or equivalency to heparin. Citrate anticoagulation, in particular, may cause hypocalcemia and death if calcium replacement is inadequate and significant metabolic alkalosis if the dialysate bicarbonate concentration is not decreased,[226] although a simplified treatment protocol may render it safer.[237] In the rare case of confirmed heparin induced thrombocytopenia, low molecular weight heparin, hirudin, argatroban, and citrate anticoagulation have been used with varying success.[226,236] Finally, substituting citric acid for acetic acid in the dialysate with concomitant heparin use during dialysis improves clearance and increases dialyzer reuse, presumably because of decreased clotting.[238,239]

On-Line Monitoring of Clearance, Hematocrit, and Access Flow

Urea concentration, hematocrit, and access blood flow may be measured on-line, that is, during the dialysis. Although the equipment and effort are expensive at present, they may prove cost-effective in the long run by improving patient care. Monitoring can minimize the amount of blood drawn and allow more sensitive and frequent assessment of adequacy, control of ultrafiltration, and detection of vascular access stenosis.

Monitoring Clearance

On-line monitoring of urea kinetics may provide the best assessment of urea removal and dialysis adequacy.[218,240–242] Available monitors include those that sample dialysate continuously or periodically to measure urea concentration[147,148,218,243,244] and those that monitor dialyzer sodium clearance by pulsing the dialysate sodium concentration and measuring conductivity.[218,245] The on-line methods for monitoring urea kinetics provide Kt/V_{urea} based on whole-body urea clearance, not just dialyzer clearance.

Monitoring Hematocrit

The hematocrit can be measured during dialysis, using either a conductivity method[246] or an optical technique.[247–249] These methods may benefit dialysis patients prone to hypotension and cramping because these symptoms are usually caused by intravascular volume depletion, which is reflected by the degree of hemoconcentration.[248] By monitoring the hematocrit on-line, the filtration rate can be varied during dialysis to minimize the magnitude of hemoconcentration and the occurrence of symptoms during dialysis.[247,249]

Monitoring Access Flow

Vascular access failure is a major problem, costing millions of healthcare dollars each year and diminishing the patient's quality of life,[250,251] prompting the National Kidney Foundation to issue management guidelines.[252] If impending access thrombosis can be predicted, the opportunity to intervene with angioplasty or surgery is available to prevent thrombosis and to extend access function. Many techniques have been described, including measuring venous pressures and determining access recirculation. Unfortunately these techniques have not prevented access thrombosis[250,251,253] because the venous pressure technique is unable to detect inflow and mid-graft stenosis[254] and because access recirculation calculated using peripheral venous blood is actually an artifact of solute disequilibrium.[166,169,165,250,255] The indicator dilution techniques for measuring access blood flow noninvasively during hemodialysis have strong predictive power and may allow timely intervention.[256–260] Observational studies[261–266] suggest that an absolute vascular access blood flow of less than 600 ml/min and a 25% decrease in access flow strongly predict vascular access failure within 3 to 12 months. Angioplasty prompted by a decrease in access flow is effective in prolonging fistula survival and preventing thrombosis, but prospective studies of surveillance and angioplasty in arteriovenous grafts have shown mixed results (for more details, see Chapter 21).[259,260,267–270] However, because preemptive correction of a stenosis before the access clots is shorter, less expensive, and decreases the risk for a missed dialysis treatment or a temporary dialysis catheter, access surveillance and intervention is still preferred in the absence of conclusive evidence for improved graft survival.[252,271,272]

DIALYSIS-RELATED COMPLICATIONS

Hemodialysis is now much safer than in the past, and many dialysis centers have administered over one million treatments without a single death attributable to the dialysis itself. Many technical advances that include fail-safe devices have reduced but not completely eliminated complications resulting from the dialysis procedure itself (see Chapter 24). A rare patient experiences an anaphylactoid or allergic reaction during the first few minutes of hemodialysis from exposure to the sterilant ethylene oxide or plasticizers present in the dialyzers or from reactions to the less biocompatible dialyzers (see Chapter 24). Bioincompatible dialyzers activate complement, cytokines, leukocytes, and platelets, causing chest pain, shortness of breath, and sludging of leukocytes and platelets in the pulmonary vasculature.

Fever during dialysis may be caused by bacterial contamination or endotoxin in the source water or dialysate and by access infection. Shear forces induced by rapid blood flow in dialysis catheters can release bacterial products and biofilm from within the catheter lumens, causing a septic shock like syndrome that can be fatal.[203] Rapid removal of solutes may cause a *dysequilibrium syndrome* that has been attributed to brain swelling: fatigue, light-headedness, and decreased ability to concentrate when mild; and altered mental status, seizures, and death when severe (see Chapter 24).

Potentially life-threatening complications such as *hemolysis* and *air embolism* are rare but must be recognized promptly. Symptoms of hemolysis and air embolism may be nonspecific and include chest pain or tightness and shortness of breath, symptoms that are also observed with reactions to the dialyzer, the sterilant, or endotoxin. In addition, the patient with air embolism may lose consciousness and seize if air has embolized to the cerebral circulation. The best treatment for both of these complications is prevention. Proper functioning of the dialysis machine and the built-in monitoring devices prevents dialysate overheating and hypotonicity that may lead to hemolysis and allows detection of air in the dialysis circuit from a leak in the system or accidental disconnection. Adequate monitoring of water quality and reused dialyzers allows detection of contaminants such as formaldehyde, bleach, chloramine, or nitrates, which can cause hemolysis (see Chapter 24).

FUTURE CONSIDERATIONS

More than 40 years of experience have demonstrated that thrice weekly hemodialysis is not completely successful in reversing the syndrome of uremia. Reasons for this are not entirely clear, but they almost certainly include the residual syndrome (see earlier discussion). Failure to eliminate the residual syndrome may be related to inadequate dialysis, failure of dialysis to reproduce one or more functions of the native kidney, or complications derived from the dialysis treatment itself.

The discovery of dialysis amyloidosis and the subsequent identification of β_2-microglobulin as the amyloid precursor represent a major advance in the battle to sustain and maintain a reasonable quality of life over an extended number of years on hemodialysis.[46] Because β_2-microglobulin is a relatively large molecule that is not removed by cellulose membranes, its discovery prompted an investigation into the more permeable high-flux dialysis membranes. Accumulated evidence shows increasingly strongly support for the use of synthetic high-flux membranes to prevent clinical progression of dialysis amyloidosis.[46]

The ever-changing landscape of the residual syndrome now encompasses adynamic bone disease, uncovered during efforts to improve the understanding and treatment of hyperparathyroid bone disease. Other battle fronts in the effort to improve the quality of life include studies of nutrition; the cause of the acute-phase response in dialysis patients; the complex interaction between the acute-phase response, nutrition, and atherosclerosis;[67,68] and methods to prevent both protein and calorie malnutrition.[65,273] Understanding the mechanisms responsible for accelerated atherosclerosis and myocardial dysfunction in dialysis patients may be a key to improving the high mortality from cardiovascular disease.

The HEMO Study suggests that increasing the urea clearance (Kt/V) above 1.3 during thrice weekly dialysis, and enhancing clearance of larger molecular molecules do not alleviate the residual syndrome.[79] In contrast, accumulating data from daily home hemodialysis indicate that blood pressure and serum phosphorus are significantly improved, often while reducing medications. Cardiac hypertrophy, heart failure, sleep patterns, and other quality of life markers also show signs of improvement, further correcting the residual syndrome.[274–280] Because the goals for future deployment of hemodialysis include reducing the need for travel to and from the dialysis center and shortening the time required for preparation and administration of hemodialysis, home hemodialysis, especially at night or during sleep, has obvious advantages. Maintaining or improving work conditions for staff managing hemodialysis patients is justifiable in itself, but is especially important in dialysis centers because a positive attitude in the staff promotes better tolerance of dialysis by the patient.

A full list of references are available at www.expertconsult.com.

VASCULAR ACCESS

Chapter 21

Bradley S. Dixon, M.D. and Laura M. Dember, M.D.

HISTORY OF VASCULAR ACCESS

The inception of hemodialysis for the treatment of patients with acute renal failure occurred with temporary access to the circulation in 1943.[1] However, the development of maintenance hemodialysis for the treatment of end-stage renal disease (ESRD) required repeated access to the circulation. This became feasible with the introduction of the external arteriovenous (AV) Quinton-Scribner shunt in 1960.[2] The pioneering accomplishments of Willem Kolff and Belding Scribner in the development of dialysis were recognized with the Lasker Award for General Medical Research in 2002. The Quinton-Scribner shunt, made of Silastic tubing connected to a Teflon® cannula, developed frequent problems with thrombosis and infection, and typically functioned for a period of months. In 1966, Brescia, Cimino, and colleagues developed the autogenous AV fistula, which remains the hemodialysis access of choice today.[3] Interpositional AV bridge grafts were developed in the late 1960s and 1970s. Early graft materials included autogenous saphenous veins, bovine carotid arteries, and human umbilical veins. In the late 1970s, synthetic bridge grafts made of expanded polytetrafluoroethylene (ePTFE) were introduced.[4,5] The ePTFE grafts can be placed in the majority of patients, are able to be used within weeks of surgical placement, and are relatively easy to cannulate. The ePTFE grafts continue to be a highly prevalent permanent dialysis access in the United States.

The use of catheters for hemodialysis access also parallels the history of dialysis. In 1961 Shaldon and associates first described femoral artery catheterization for hemodialysis access.[6] Uldall and associates first reported the use of guidewire exchange techniques and subclavian vein puncture for placement of temporary dialysis catheters in 1979.[7] In the late 1980s the use of surgically implanted tunneled, cuffed, double-lumen catheters was introduced.[8] Subcutaneous vascular ports were introduced as an alternative to the cuffed tunneled catheter in the 1990s; however, their use has not become widespread.[9] The major use of catheters for hemodialysis access is as a bridging device to allow time for maturation of a more permanent access, or for patients who need only temporary vascular access. However, the use of catheters for prolonged periods because of exhaustion of sites for AV access placement or because of AV fistula maturation failure is becoming increasingly frequent and is a source of concern among the nephrology and vascular surgery communities.

There is general consensus that autogenous vein AV fistulae are preferable to other currently available vascular access options. Current clinical practice guidelines recommend that patients with chronic kidney disease should be referred for creation of an autogenous AV fistula at least 6 months before the anticipated initiation of dialysis.[10]

Access-Associated Morbidity and Practice Patterns

The rapid growth of end-stage renal failure programs in the United States and worldwide has been accompanied by a tremendous increase in hemodialysis vascular access-associated morbidity and cost. Indeed, vascular access continues to be referred to as the *"Achilles Heel"* of the hemodialysis procedure.[11] Within the Medicare program, the annual costs of creating, maintaining, and replacing vascular access is estimated to exceed one billion dollars.

The importance of vascular access care has been emphasized by data from the United States Renal Data System (USRDS) and other sources demonstrating that adjusted relative mortality risk is substantially higher for patients with a central venous catheter (CVC) compared to an AV fistula.[12–16] Both infectious and cardiovascular causes have been implicated in the mortality risk. For diabetic patients, the use of AVGs is also associated with significantly higher mortality risk compared to AV fistulae (Figure 21-1).[12]

Patterns of vascular access usage differ between Europe and the United States. A report from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in 2002 compared vascular access use and survival in Europe and the United States and found that autogenous AV fistulae were used by 80% of European patients compared to 24% of prevalent dialysis patients in the United States.[17] AV fistula use was significantly associated with male sex, younger age, lower body mass index (BMI), absence of diabetes mellitus, and a lack of peripheral vascular disease. However, even after adjustment for these risk factors, there was a 21-fold increased likelihood of AV fistula use in Europe versus the United States. A follow-up study from DOPPS suggests that predialysis care by a nephrologist does not account for the substantial variations in the proportion of patients commencing dialysis with an AV fistula, and that the time to fistula cannulation after creation also varies greatly between countries.[18] More recent studies suggest that for some countries that historically had had high prevalence of AV fistulae, the use of AV fistulae has started to decline somewhat.[19,20] The reasons for the decline are not clear but are not fully attributable to patient characteristics.

Within the United States, substantial variation between facilities in vascular access types has been noted with the prevalence of AV fistulae ranging from 0 to 87%.[17] There is also large variation in access type by geographic region, sex, and race within the United States.[21] Thus practice pattern variations in vascular access are determined by local preference, in addition to patient-related factors.

Data from Medicare and the USRDS indicate that AV fistula use is increasing in the United States. The increase in AV fistula placement began following the publication of the National Kidney Foundation/Dialysis Outcomes Quality Initiative (K/DOQI) Guidelines in 1997[22] and has continued with efforts by the Centers for Medicare and Medicaid Services.[23] Over the past decade, AV fistula prevalence in the United States increased from approximately 20% to approximately 44% but still falls below the current CMS goal of 66%.[23,24] Unfortunately, the increase in AV fistula use has been accompanied by an increased reliance on catheters for hemodialysis vascular access. Currently 82% of patients in the United States start dialysis with a CVC and 19%-25% use a CVC as their permanent access.[24,25] CVC use has also been increasing in many other countries. Thus considerable challenges remain in attempting to optimize vascular access practice patterns in the future.

AUTOGENOUS ARTERIOVENOUS FISTULA

Construction

The autogenous AV fistula is constructed by a direct surgical anastomosis between an artery and nearby vein. Exposure of the vein to arterial blood flow results in dilatation of the lumen and thickening of the vein wall, a process referred to as maturation. Maturation must be adequate to allow frequent needle cannulation and to support the blood flow of the dialysis circuit. Fistula maturation usually takes 6–16 weeks.

Upper extremity fistulae can be created in the forearm or the upper arm (Figure 21-2). The Brescia-Cimino fistula, created through an anastomosis of the radial artery and cephalic vein at the wrist, was the first type of autogenous

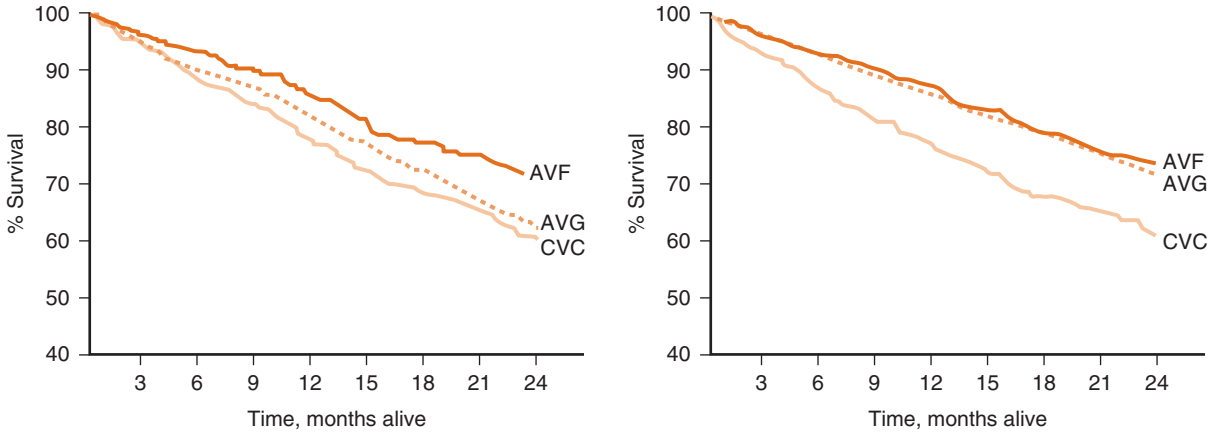


FIGURE 21-1 Adjusted patient survival based on dialysis access type. *AVF,* arteriovenous fistula; *AVG,* arteriovenous graft; *CVC,* cuffed venous catheter. Left graph, diabetic patients; right graph, nondiabetic patients. (Reproduced with permission from R.K. Dhingra, E.W. Young, T.E. Hulbert-Shearon, et al., Type of vascular access and mortality in U.S. hemodialysis patients, Kidney Int. 60 [2001] 1443-1451.)

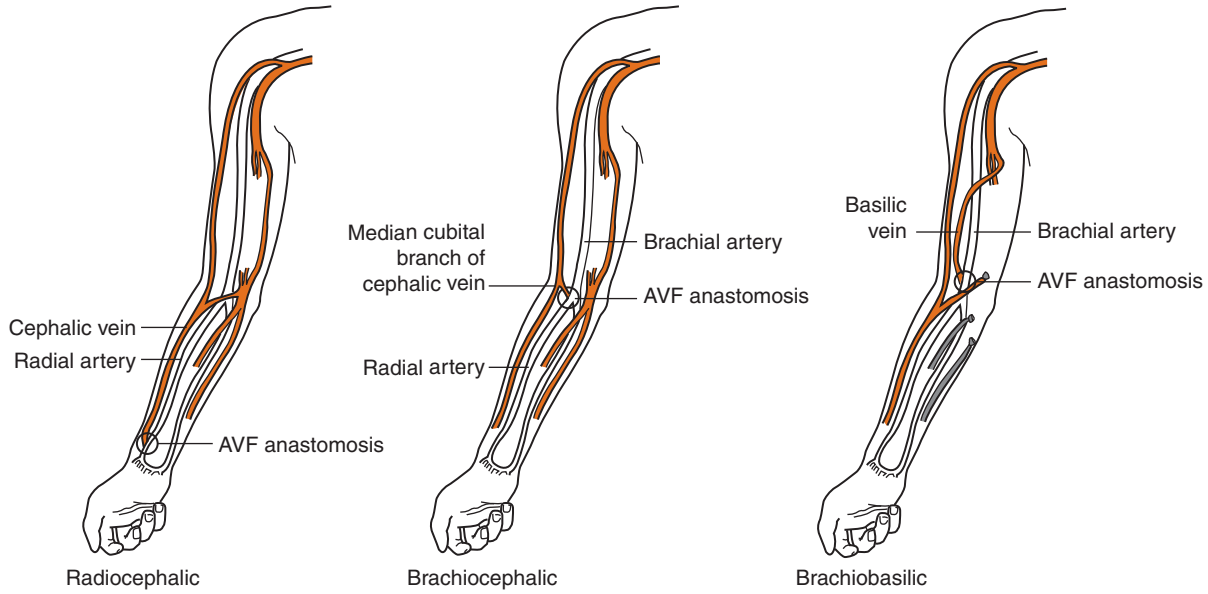


FIGURE 21-2 Types of autogenous fistulae. (Adapted with permission from M. Allon, M.L. Robbin, Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions, Kidney Int. 62 [2002] 1109-1124.)

fistula described and is the fistula that should be considered initially in a patient who has not had a previous forearm AV access.[3] Ulnar artery-basilic vein and radial artery-basilic vein anastomoses are additional approaches for creating a forearm fistula that are used relatively infrequently. In the upper arm, construction of the brachial artery-cephalic vein fistula is the most straightforward from a surgical standpoint. However, because many patients have had multiple prior cannulations of the cephalic vein in the antecubital space, stenoses are often present that preclude use of the vein for an upper arm fistula. An alternative is the brachial artery-basilic vein fistula. Construction of a brachiobasilic fistula requires dissection and subcutaneous tunneling of the basilic vein to reposition it superficially and laterally and thereby enable needle cannulation. Thus the creation of a brachiobasilic fistula (often referred to as *"basilic vein transposition fistula"*) is relatively laborious, but its use is becoming more widespread as its favorable short-term and long-term outcomes are increasingly recognized.[26,27] At most centers, the creation of the anastomosis and the transposition of the vein are performed during a single surgical procedure. Some surgeons prefer a two-step procedure in which the vein repositioning is performed several weeks after the anastomosis creation.[28] The potential advantage of the two-step approach is that damage to the vein during dissection and tunneling is reduced because of the remodeling that has occurred during the preceding weeks.

Fistulae can be constructed with an end-to-side or a side-to-side vein-artery anastomosis. Advantages of the end-to-side anastomosis, which is probably the technique used most often, include the ability to create a 90-degree rather than an acute-angle anastomosis, reduced likelihood of venous hypertension in the distal extremity, and the ability to bring together vessels that are far apart. Side-to-side anastomoses are technically easier to create. However, they may require ligation of the vein distal to the anastomosis to prevent hand swelling. Moreover, the acute angle between the vessels that results from a side-to-side anastomosis is associated with increased turbulence that may contribute to development of stenosis.[29] End-to-end anastomoses are usually avoided because of the risk of distal extremity ischemia with arterial ligation.

Advantages of the Autogenous Fistula

Multiple studies indicate that rates of thrombosis and need for salvage procedures are substantially lower for autogenous fistulae than for synthetic grafts.[24,30–33] Cumulative survival, meaning survival until access abandonment, has also been shown in several analyses to be better for fistulae than grafts despite aggressive and often successful efforts to restore patency of thrombosed grafts.[30] It should be recognized that many of the studies comparing outcomes of grafts and fistulae did not include primary failures, that is, accesses that fail before ever being used for dialysis. It has been suggested that if primary failures are included in such analyses, the cumulative survival of fistulae and grafts are similar.[26,34] Nonetheless, there is general agreement that once mature, a fistula is much less likely than a graft to require intervention. An additional important advantage of AV fistulae is the substantially lower rate of infections compared to grafts. For these reasons, one of the major recommendations of the K/DOQI Clinical Practice Guidelines is to increase the prevalence of autogenous fistulae.[10]

An additional potential but unproved advantage of the autogenous fistula is that it does not contribute to the chronic inflammatory state evident in a large proportion of patients on maintenance dialysis. With accumulating evidence implicating chronic or recurrent inflammation in the ESRD-associated cardiovascular disease, it is reasonable to infer that the use of autogenous vessels rather than synthetic material for vascular access may provide benefits that extend beyond reducing vascular access complications themselves.

Why the Low Prevalence of Autogenous Fistulae?

Despite widespread recognition of its advantages, only approximately 40% of patients in the United States receive hemodialysis through an autogenous fistula.[10,24] Historically, two interrelated factors have contributed to the low prevalence of autogenous fistulae: 1) the widespread practice of initially placing a graft rather than attempting construction of an autogenous fistula, and 2) the high rate of primary failure of autogenous fistulae. The tendency to place synthetic grafts before attempting autogenous fistula construction evolved because of the ability to use grafts soon after surgery, the good short-term outcomes in patients with vessels that appear unsuitable for fistula construction, referral of patients to nephrologists when dialysis initiation is imminent rather than earlier in the course of the renal disease, and the technical ease of graft placement relative to fistula creation, particularly when vein transposition is needed.[11,35] Although some of these factors are not readily modifiable, wide geographic variations in fistula prevalence suggest that clinical practice patterns are important contributors to the types of accesses created.[36] Reports from centers that have implemented multidisciplinary access programs involving nephrologists, vascular surgeons, and dialysis staff suggest that substantial increases in fistula creation attempts can be achieved, and that the higher attempt rates are accompanied by increases in the prevalence of functioning fistulae (Table 21-1).[37,38] The recent emphasis on fistula creation does appear to have altered practices such that initially placing a graft rather than attempting construction of an autogenous fistula has become less frequent.

In order to be able to be used for dialysis an autogenous fistula must mature, meaning the blood flow and vessel diameter must increase sufficiently to allow repeated cannulation and support the dialysis blood circuit.[39] Single-center series published during the past 10 years suggest that 20%-50% of newly created fistulae are never able to be used for dialysis (primary failure) because of inadequate maturation.[35] A recent large multicenter clinical trial found that approximately 60% of new fistulae did not mature sufficiently for use.[40] Maturation failure can be the result of thrombosis, inadequate arterial or venous dilation, stenosis, or accessory veins.[39] Demographic and clinical factors found in some, but not all, studies to be associated with primary failure include older age, female sex, black race, obesity, diabetes mellitus, cardiovascular disease, peripheral arterial disease, and low blood pressure.[41–43] Although the biological processes involved in fistula maturation are not fully understood, it is likely that functional and anatomical characteristics of the vessels used for fistula creation are important determinants of maturation outcomes. Attempts to identify serological or other biochemical predictors of fistula failure have not been revealing.

TABLE 21-1 Components of a Multidisciplinary Autogenous Fistula Program

TEAM MEMBERS
Nephrologists
Dialysis nurses and patient care technicians
Vascular surgeons
Interventional radiologists
Vascular ultrasonographers
Vascular access coordinator
GOALS
Early placement of vascular access
Creation of upper arm and transposition fistulae if radiocephalic fistula is not possible
Vascular mapping for identification of suitable vessels
Replacement of failed synthetic grafts with autogenous fistulae
Salvage interventions for fistula maturation failures
Reduction in duration of central venous catheter use
APPROACHES
Develop consensus regarding goals of program
Prospective tracking of vascular access types and outcomes
Active monitoring of fistula maturation after anastomosis creation
Ongoing education of patients and dialysis facility staff
Ongoing dialogue among team members to modify approaches

Assessment of Vessel Quality

There are several approaches to evaluating vessels preoperatively to identify those that are suitable for fistula creation. The simplest method is physical examination of the veins before and after placement of a tourniquet proximally. Although this allows assessment of the diameter of superficial veins, it does not identify proximal stenosis or thrombosis that could interfere with fistula maturation. In addition, physical examination may fail to identify deeper veins that would be suitable if transposed and thus could lead to an inappropriate decision to place a graft rather than attempt fistula creation. More information about the vasculature can be obtained with ultrasonography or venography, (i.e., vascular mapping). Ultrasound evaluation of the extremity provides information about vein diameter and the presence of stenosis, thrombosis, and sclerosis. In addition, characteristics of the artery such as diameter and flow can be assessed. Vascular mapping with ultrasonography is time-consuming and operator-dependent and is most successful when a specific protocol is followed to ensure uniform measurements and reporting by multiple operators (see example of one such protocol in Table 21-2). Venography also provides information about vessel size and patency and probably is better for identification of stenoses and assessment of central vessel patency than is ultrasound. However, venography does not enable evaluation of arteries, it exposes patients to contrast, and carries the risk of vein damage from cannulation or phlebitis that could render the vein unsuitable for fistula construction.

Several studies have demonstrated increases in rates of attempted fistula creation after implementation of preoperative vascular mapping protocols.[44–46] In most of these studies, the increased rates of fistula creation attempts were accompanied by a reduction in the primary failure rates, and among those studies that reported it, an increase in the fistula prevalence at the center. None of these studies was a randomized, controlled trial, and it is possible that the improvements seen were due to factors other than vascular mapping such as changes in surgical approaches, better preoperative protection of vessels, or earlier referral for access creation. Thus although preoperative vascular mapping provides a substantial amount of information about vessel quality and is generally recommended, its ultimate impact on fistula outcomes is not clear.

TABLE 21-2 Example of a Protocol for Vascular Mapping Using Ultrasonography[1]

1. Examine **radial artery** at wrist for flow, peak systolic velocity, quantitative blood flow (should be ≥10 ml/min) and diameter (should be ≥2 mm).
2. Examine **ulnar artery** at wrist for flow, peak systolic velocity, quantitative blood flow, and diameter (should be ≥2 mm).
3. Examine **brachial artery** just above antecubital fossa for peak systolic velocity, quantitative blood flow, and diameter (should be ≥2 mm).
4. Place tourniquet at upper forearm. Examine **cephalic vein** at wrist.
   a. Measure diameter at wrist (should be ≥2.5 mm).
   b. Follow to elbow, and examine for stenoses or occluded segments. Measure diameter at mid and upper forearm.
5. Place tourniquet at upper arm. Examine cephalic vein above elbow:
   a. Measure diameter of vein above elbow at low, mid, and upper arm (should be ≥2.5 mm).
   b. Follow to shoulder and examine for segmental stenoses or occluded segments.
   c. Determine whether vein is superficial for most of its course (within 1 cm of skin).
6. Examine **basilic vein** in upper arm:
   a. Measure diameter of vein above elbow at low, mid, and upper arm (should be ≥2.5 mm).
   b. Follow to axilla and examine for segmental stenoses or occluded segments.
7. Remove tourniquet. Examine subclavian and internal jugular veins for stenoses or occlusions.

[1]Protocol used at Boston University Medical Center.

There is a growing interest in the impact of functional characteristics of vessels on fistula maturation.[39] A small study found that venous distensibility as measured by occlusion plethysmography before fistula creation correlated with maturation outcomes.[47] It is anticipated that additional studies of arterial function in addition to venous function will be available during the upcoming few years.

Selection of the Location for Autogenous Fistula Creation

In general, it is preferable to use the distal extremity for initial AV access placement and move to more proximal sites, if necessary. It is also usually preferable to use the nondominant arm to limit the functional disability that might occur with perioperative complications such as vascular steal syndrome or peripheral neuropathy. Thus if the forearm vessels appear suitable, a radiocephalic fistula in the nondominant arm should be created as the initial access.

Decisions about access type and location are less straightforward if the forearm vessels do not appear suitable for an autogenous fistula, or if a forearm autogenous fistula is created initially but fails. Until recently, the approach by many nephrologists and/or surgeons was to place a forearm AV graft in these situations. However, with the recognition of the long-term benefits of autogenous fistulae, and recent studies suggesting a lower primary failure rate for upper arm than forearm fistulae, many now prefer to create an upper arm fistula as an initial access in individuals who do not have suitable forearm vessels.[48] Whether such an approach is preferable to that of initially placing a forearm graft and subsequently creating an autogenous fistula in the upper arm if the graft fails, is debated.[34] A potential advantage of the latter approach is that alterations in upper arm veins that occur as a result of increased flow through the forearm graft could ultimately enhance the suitability of the upper arm veins for autogenous fistula creation.

Preoperative Preparation for Autogenous Fistula Creation

Because the quality of the vein is so critical to successful autogenous fistula creation, every effort should be made to protect the veins in the extremity that will be used for access creation. Venipuncture for obtaining blood specimens and intravenous catheter placement should be avoided at sites proximal to the planned AV anastomosis. Ideally, fistula creation should be performed many months before vascular access use is required to prevent the need for CVC placement and the associated risk of central vein stenosis. These measures for preserving vein quality are more feasible for patients undergoing initial access placement than for those who have already had multiple failed accesses.

Pharmacological Approaches to Improving Autogenous Fistula Outcomes

There are currently no pharmacological interventions that have been clearly demonstrated to improve the maturation or longevity of autogenous fistulae. Several studies have evaluated the efficacy of antiplatelet agents for preventing early thrombosis of autogenous fistulae.[49] In small, underpowered studies ticlopidine, microencapsulated aspirin, and sulfinpyrazone all reduced early thrombosis. The findings of these studies provided the basis for a large clinical trial of the antiplatelet agent, clopidogrel, for prevention of early thrombosis of new autogenous fistulae.[40] In this double-blind, placebo-controlled trial, 877 patients were randomized to clopidogrel or placebo for 6 weeks starting within one day following fistula creation. The risk of thrombosis within 6 weeks, the primary outcome of the trial, was reduced by clopidogrel (relative risk 0.63; 95% confidence interval 0.46–0.97; P=0.018). However, the reduced thrombosis rate was not accompanied by an increase in the proportion of fistulae that were usable for dialysis, suggesting that early thrombosis may be a manifestation rather than cause of maturation failure. The findings of this trial do not support the routine use of clopidogrel for preventing early failure of autogenous fistulae. Novel approaches to enhancing fistula maturation such as local delivery of pharmacological agents, cell-based treatments, and gene therapy are under active investigation.

Initial Cannulation of New Fistulae

Premature cannulation of autogenous fistulae predisposes to infiltration and compression of the vein from extravasated blood that can result in fistula thrombosis. Thus careful examination of the fistula by experienced team members should be performed before the initial use, and additional

time for maturation should be used if the fistula appears unsuitable or if initial attempts at use are unsuccessful. Specific recommendations about when to initiate cannulation vary. Data from the DOPPS suggest that in some countries, fistula cannulation within 4–6 weeks after creation is common and is not associated with reduced fistula survival.[18] Given the substantial long-term benefits of a functioning fistula, it is advisable to exercise caution with regard to early use of new fistulae. However, such caution should be balanced with the risks associated with extended use of catheters.

Salvage of Failing Fistulae

Regular examination of new fistulae should begin early after anastomosis creation to evaluate the maturation process. Two potentially modifiable causes of maturation failure are stenosis of the draining vein and the presence of vein branches that decrease the blood flow through the draining vein.[39] Balloon angioplasty of identified stenoses can enhance maturation as can surgical ligation of vein tributaries.[50,51] Because the use of radiographic contrast may hasten the need for initiation of dialysis, ultrasonography may be preferable to angiography as the diagnostic study for patients who have not yet started dialysis. Surgical superficialization can convert a deep fistula that has matured adequately but is unsuitable for use because of cannulation difficulty to an effective vascular access.

In many centers, surgical or radiological thrombectomy of a thrombosed fistula is not attempted because of the technical difficulties and poor outcomes. However, recent reports suggest that with innovative approaches, percutaneous declotting of mature autogenous fistulae can be performed with reasonable success rates.[52,53] Salvage is rarely applied to fistulae that thrombose within the first few weeks after creation; such fistulae are usually abandoned.

Monitoring Mature Fistulae for Stenoses

For fistulae that have matured successfully, stenosis development is less frequent than for synthetic grafts, and the use of routine monitoring for fistula stenosis has not been established.[54] In contrast to grafts, in which the majority of stenoses occur at the graft-vein anastomosis downstream of where needle cannulation for dialysis occurs, stenoses in fistulae most often occur upstream of the dialysis needles near the AV anastomosis. Thus if monitoring is used, determination of access blood flow or Doppler ultrasound examination is a more appropriate method than venous pressure measurement.

Complications of the Autogenous Fistula

Steal Syndrome

Impaired perfusion of the extremities below the level of the vascular access is a serious and debilitating complication that can occur after placement of either an AV fistula or graft.[55] Distal ischemia occurs when the low resistance shunt accommodates more flow than can be delivered by antegrade flow through the inflow artery feeding the fistula.[56] In this case, the fistula also "steals" blood from the artery below the fistula (Figure 21-3). This retrograde flow lowers the perfusion pressure in the distal extremity, and if this falls below a critical level, it will lead to tissue ischemia. Steal syndrome occurs predominantly in individuals with underlying vascular disease, and its incidence may be increasing with the growing proportion of elderly and diabetic patients comprising

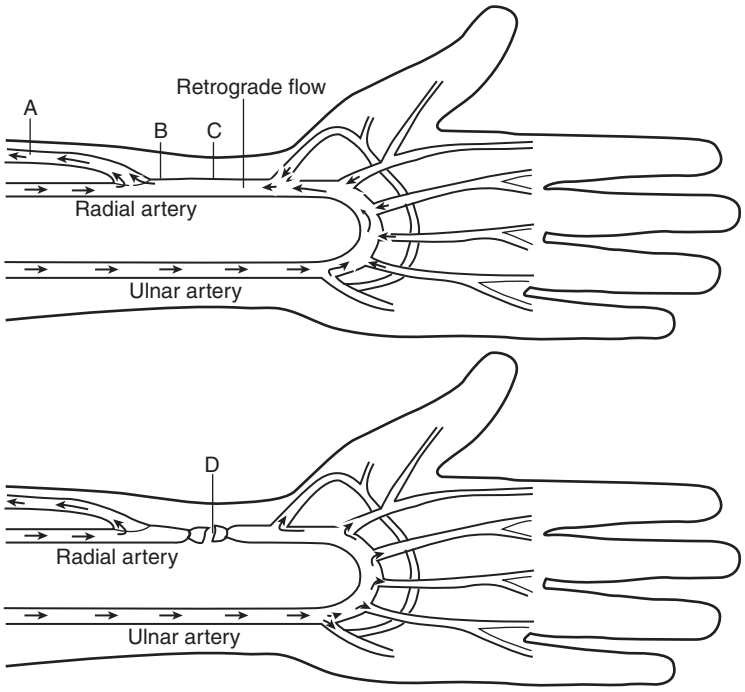


FIGURE 21-3 Pathogenesis of arteriovenous steal. Steal occurs when the arteriovenous fistula (*A*) receives both antegrade and retrograde (*C*) flow from the radial artery. (*B*) is the arteriovenous anastomosis.) Steal can be corrected by ligation of the radial artery below the fistula (*D*), but it may lead to inadequate fistula flow. (Adapted from A.M. Miles, Vascular steal syndrome and ischaemic monomelic neuropathy: two variants of upper limb ischaemia after haemodialysis vascular access surgery, Nephrol. Dial. Transplant. 14 [1999] 297-300.)

the ESRD population. With a fistula, steal syndrome usually develops gradually over several weeks after creation of the surgical anastomosis as the fistula blood flow increases with progressive vein maturation. In contrast, severe arterial compromise can occur immediately after graft placement.

Ischemic monomelic neuropathy, a syndrome characterized by acute pain, weakness, and paralysis of the extremity often in association with sensory loss is a rare complication occurring in patients who get an upper arm access involving the brachial artery.[57] In contrast to the classic steal syndrome, the radial pulse is usually palpable and digital pressure is usually greater than 50 mmHg. The patients are typically diabetic, older, and with preexisting neuropathy or vascular disease. Symptoms occur immediately or within hours after access placement and are very difficult to reverse unless the problem is recognized and treated immediately by access ligation before further irreversible damage occurs.[57]

Mild symptoms of steal occurring shortly after access placement can be treated symptomatically and observed.[55] In more severe cases, ligation of the access will cure the problem but leaves the patient without an AV access for dialysis. A number of approaches have been suggested to deal with access steal while leaving the access intact for dialysis.[55] Stenosis in the artery proximal to the fistula must first be excluded or treated before diagnosing access steal syndrome. Measurement of access blood flow rate is important in planning the intervention. Banding or plicating the fistula until pressure in the hand is measured to be above 50 mmHg has been used successfully but reduces access flow and can predispose to thrombosis. The distal revascularization-interval ligation (DRIL) procedure involves ligating the artery distal to the fistula and using a vein graft bypass from the inflow artery above the fistula to a site on the artery just below the ligation.[58] The procedure is quite effective if the preoperative access flow is not too low; however, it places the distal limb at risk of ischemia if the vein graft fails. An alternate that avoids this problem is the *'revision using distal inflow'* (RUDI) procedure.[59] In the RUDI procedure, the fistula is ligated and a vein graft used to extend the fistula to a smaller artery in the distal arm. However, this is a complicated procedure that leads to a reduction in overall access blood flow. Another approach for fistulas with low flow associated with vascular steal syndrome is *"proximalization of arterial inflow"* (PAI).[60] In this approach the fistula is ligated and a prosthetic 6 mm graft coming off a more proximal site of the brachial or axillary artery is anastomosed to the previous access outflow vein. Access flow is increased, but a fistula is converted into a graft.

Heart Failure

High output cardiac failure that resolves with closure of the AV shunt is a well-documented but rare complication of AVGs and autogenous fistulae.[61] The greatest risk appears to be in people with underlying organic heart disease and an autogenous fistula placed in the upper arm (e.g., brachiocephalic fistula).[61] However, high output failure has been reported with ePTFE grafts.[62]

Blood flow in a functional hemodialysis access generally runs between 0.75 to 2.5 liters per minute with occasional patients having blood flows greater than 4 liters per minute.[48,63] Most patients can maintain this access blood flow over many years without developing clinical evidence of heart failure. However, this high access flow may contribute to the development of LVH in some patients.[64] Many patients with an AV shunt also demonstrate an increase in pulmonary artery pressure. In the presence of underlying lung disease or primary pulmonary hypertension, this could exacerbate right heart failure.[65]

Measurement of access blood flow by itself does not identify those with existing or impending high output failure.[66] A drop in heart rate of 7 bpm or more after shunt closure is one sign (Nicoladoni-Branham sign) used to detect a hemodynamically significant shunt but may be absent in dialysis patients with high output failure. If the shunt blood flow significantly exceeds the drop in cardiac output observed after temporary shunt occlusion, that may also be an indication of high output failure.[66] However, this observation needs further validation. An access blood flow to cardiac output ratio above 0.3 has been suggested as a risk factor for heart failure, but there is currently no well-validated tool to predict who will develop symptomatic heart failure after access placement, and this remains a clinical judgment.[67] Development of symptomatic heart failure after access placement can be treated by reducing access blood flow with banding, placing a tapered AVG or moving the arterial inflow distally (e.g., RUDI procedure), but often requires ligation of the access.

Aneurysm and Pseudoaneurysm

True aneurysms occur when the vessel wall becomes weak and dilates. Pseudoaneurysms occur as a result of vessel trauma most commonly at needle puncture sites leading to a localized extravasation of fluid in which the wall is composed of perivascular adventitia, fibrous tissue, and hematoma. Most commonly the etiology for these aneurysms is *"one site-itis"* in which there are frequent repetitive needle sticks into one or two regions of the access. Buttonhole cannulation of the same holes during every dialysis session using blunt needles has been suggested as a strategy to reduce aneurysm formation. Infection may also be a cause of aneurysm formation particularly in biografts. Aneurysms and pseudoaneurysms occur more commonly in biografts than in the currently used reinforced synthetic grafts. Aneurysms and pseudoaneurysms that occur in fistulas or grafts can be surgically repaired to preserve the access site for future use. Both true aneurysms and pseudoaneurysms can limit sites for needle placement and can rupture if the overlying skin is compromised.

Venous Hypertension

An increase in venous pressure is a physiological consequence of all AV shunts. If the venous valves are incompetent, then retrograde flow may result. In most cases the symptoms are mild and resolve with time. The presence of significant venous hypertension results in dilated veins, swelling of the distal extremity, and bluish discoloration of the skin. Over time, severe and persistent venous hypertension can lead to chronic venostasis changes such as thickening and discoloration of the skin and skin ulceration and pain.[68] A central venous stenosis is the most common etiology for severe venous hypertension occurring after placement of an AV shunt. Angiography of the proximal venous outflow tract and central veins is indicated. If a stenosis is located, it can be treated with angioplasty and stenting in an attempt to decrease symptoms and preserve access function.[69] In severe cases, the access may need to be ligated to preserve the extremity.

Infection

In contrast to synthetic grafts, autogenous fistulae rarely become infected. Antibiotic therapy alone is often sufficient for eradication of fistula infections although aneurysmal infections may require surgical resection because of intra-aneurysmal stasis or thrombus.

ARTERIOVENOUS GRAFTS

Terminology

For patients in whom an autogenous AV fistula cannot be constructed one option is to interpose a graft that serves as a conduit between the artery and vein. Nonautogenous arteriovenous grafts (AVGs) can either be prosthetic, such as ePTFE, a biograft, or a composite biosynthetic graft.[70] In addition, a fully autologous AVG prepared in vitro from the patient's cells has recently been described.[71] Biografts may be an autograft (i.e., from a different site in the same individual, such as the saphenous vein), an allograft (i.e., from a genetically different individual of the same species), or a xenograft (i.e., from a different species, such as a bovine vessel).

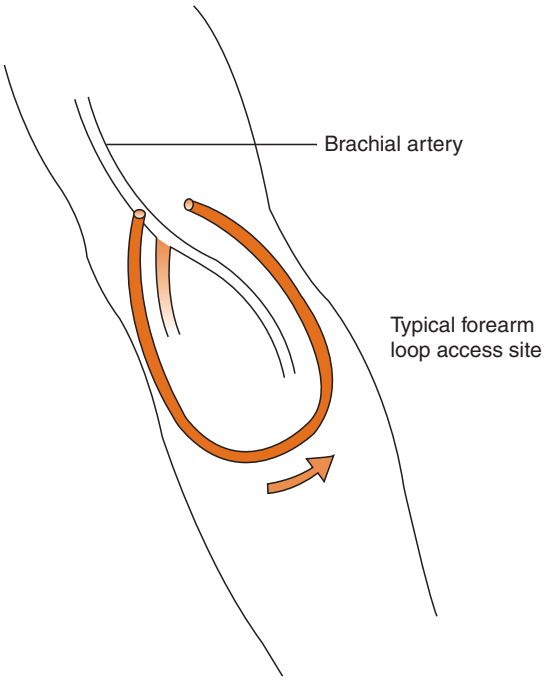


FIGURE 21-4 Configuration for typical forearm loop graft.

Graft Location and Configuration

A graft allows for selection of the optimal arterial and venous sites for surgical anastomosis and provides an easy target for cannulation. Depending on the target vessels that are available, there are a number of anatomical variations of AV graft that can be created. The forearm straight graft connects the radial artery in the forearm to the cephalic vein in the antecubital fossa. The forearm loop graft bridges the brachial artery to either the cephalic or basilic vein at the level of the antecubital fossa. Most commonly, blood flows through the forearm loop graft from medial (arterial side) to lateral (venous side) in the direction indicated by the extended thumb (*"blue thumb"*, Figure 21-4). However, the direction of flow may be reversed in some forearm loop grafts (*"red thumb"*). The surgeon needs to record this information in the patient's chart at the time of access placement. AV grafts placed in the upper arm typically join the brachial artery at the antecubital fossa with the axillary vein. If access sites have been exhausted in the arms, then a femoral loop graft may be placed in the leg. In exceptional circumstances where other options have been exhausted, heroic types of accesses have been constructed.[72] These include the necklace graft that connects the axillary or subclavian artery to the contralateral jugular or subclavian vein and the arterial interposition graft in which the artery (e.g., subclavian, femoral, or brachial artery) is transected and a loop of graft material is inserted between the proximal and distal ends.

Graft Materials

The ideal graft material would be biocompatible, nonthrombogenic, easy to cannulate, easy to surgically manipulate, low cost, resistant to infection, and able to withstand multiple cannulations without degeneration or pseudoaneurysm formation.[73] As listed in Table 21-3, many types of materials have been tried but to date the perfect graft material and design have not been found. Currently, the preferred graft material is ePTFE.[74]

In 1969 Gore discovered that polytetrafluoroethylene (PTFE), the polymer in Teflon®, could be rapidly stretched to create a strong microporous plastic called expanded PTFE (ePTFE). In 1976, Baker and colleagues reported

TABLE 21-3 Graft Materials

Synthetic grafts
Dacron velour
Sparks-Mandril graft
Polyurethane (Vectra®)
Expanded Polytetrafluoroethylene (e.g., Gore-Tex®, Impra®)
Biografts
Autograft
Saphenous vein
Allograft (cryopreserved or denatured)
Saphenous vein
Femoral vein (CryoVein®)
Umbilical vein (Dacron covered)
Xenograft (denatured)
Bovine carotid artery heterograft (e.g., Artegraft®)
Bovine mesenteric vein (Procol®)
Biosynthetic
Ovine collagen/polyester mesh (Omniflow)
Autologous tissue engineered graft
Skin fibroblasts/vein endothelial cells (Lifeline)

using ePTFE as an AV graft for hemodialysis patients.[4] Subsequent studies demonstrated that the patency and complication rate of ePTFE was equal to or better than other available synthetic grafts or biografts; hence ePTFE rapidly became the preferred choice as graft material for secondary AV access in hemodialysis patients.[74] There are several commercial types of ePTFE grafts with variations in fibril length, thickness, pore size, external support, wrappings, coatings, internal diameter, and geometry.[74] However, there is no conclusive evidence that one type of ePTFE design is superior to another.[32]

Recent studies have suggested that polyurethane is comparable to ePFTE in terms of patency and complications.[75] The Vectra® graft has an inner and outer porous layer that allows tissue ingrowth and a central core made of Thoralon, which is a self-sealing polyurethane material. The central self-sealing core reportedly allows for earlier graft cannulation after surgery without the problems of bleeding, seroma formation and thrombosis seen with early cannulation of ePTFE grafts. However, the Vectra® graft is difficult to image by Doppler ultrasound, thus making it difficult to use this technique to look for access stenosis.[76]

Recent advances in tissue engineering have led to the development of a fully autologous AV graft prepared from the patient's own cells.[71] A skin biopsy is used to grow sheets of fibroblasts in vitro that are wrapped around a stainless steel mandrel and allowed to fuse. Endothelial cells from a vein biopsy are used to seed the lumen 7 days before the graft is implanted. A proof of concept study was recently reported in 10 patients.[71] More study is clearly needed, but tissue engineered grafts offer exciting possibilities for the future.

Graft Patency

There is a wide variation in the reported long-term patency of ePTFE vascular access grafts. Recent studies demonstrate that primary failure in the United States occurs in half of all new ePTFE grafts within 6 months or less of placement, which is no better than autogenous fistulas placed in the forearm.[31,32,48,77–79] Prosthetic grafts can often be salvaged, leading to improved secondary patency rates. The better salvage rate for failed AV grafts compared to autogenous fistulae leads to nearly equivalent 1- and 2-year rates of secondary patency.[31,48,77,78] This is achieved however at the expense of significantly more graft revisions and complications. With extended follow-up beyond 2 years, autogenous fistulas maintain functional patency longer and with fewer complications than grafts.[48,78]

Graft Complications

AV steal, congestive heart failure, aneurysm/pseudoaneurysm formation, and venous hypertension are complications seen in both grafts and fistulas and were discussed previously. Thrombosis and infection are more common with grafts and are dealt with in more detail below.

Thrombosis

Thrombosis is the most common graft complication and cause of access failure. Thrombosis has been reported as the cause of 70%-95% of all graft failures.[30,78] The rate of graft thrombosis in the literature ranges from about 0.25 to 1.4 thrombotic episodes per patient-year.[78–80] The large variation undoubtedly reflects case mix, intensity of access surveillance, and local access management practices. The risk of thrombosis is greatest immediately after access placement and declines thereafter. However, the risk of thrombosis is high even in established grafts and typically exceeds 0.5 episodes per patient-year.[78–80] Abnormalities that predispose to graft thrombosis (Table 21-4) include: 1) impaired blood flow resulting from vascular stenosis and hematorheological alterations at the graft-vessel anastomosis, 2) vessel wall abnormalities including the thrombogenic graft-blood interface and endothelial damage or dysfunction, and 3) abnormalities in blood constituents including acquired or inherited abnormalities in coagulation or fibrinolytic pathways and platelet function. While most studies have focused on the role of vascular stenosis in graft thrombosis, each of these factors is interrelated and more than one factor ultimately determines whether thrombosis occurs in a given individual.

TABLE 21-4 Predisposing Factors to Graft Thrombosis

Abnormal blood flow
Vascular stenosis
Rheologic abnormalities
Abnormal vessel wall
Blood-graft interface
Endothelial damage or dysfunction
Abnormal blood constituents
Platelets
Coagulation pathway
Fibrinolytic pathway

Vascular stenosis due to neointimal hyperplasia is the most common underlying cause of thrombosis in an established graft. Based on angiographic studies, vascular stenosis exists in over 85% of thrombosed or failing grafts.[30,81] The most common site of stenosis is at the vein-graft anastomosis (Figure 21-5). However, stenoses are also found at the

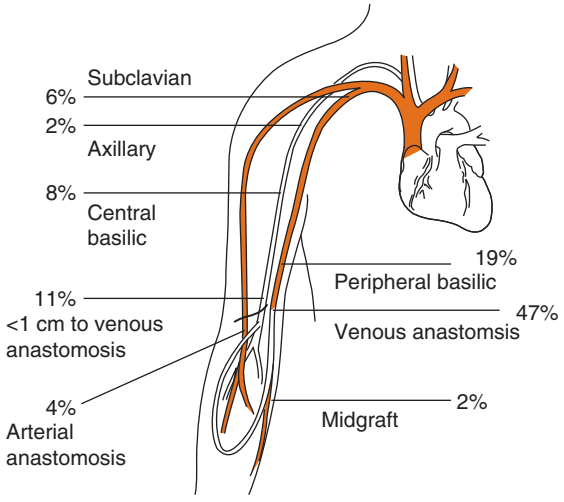


FIGURE 21-5 Location of stenosis by angiography in failing grafts. (Adapted from R.Y. Kanterman, T.M. Vesely, T.K. Pilgram, et al., Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty, Radiology 195 [1995] 135-139.)

arterial anastomosis, within the body of the graft, the downstream vein, and cephalic arch.[81,82] There are at least two mechanisms whereby stenosis can lead to thrombosis. First, a hemodynamically significant venous stenosis produces a decrease in access flow rate and an increase in intraaccess pressure.[83,84] The resulting decrease in the shear rate and altered surface tension at the blood-graft interface leads to an increased interaction of platelets and clotting factors with the surface of the graft.[85] Secondly, the stenosis itself creates an increase in blood velocity and wall shear stress at the level of the stenosis that can activate platelets and promote platelet adhesion and aggregation.[86] Hence access stenosis with its attendant alterations in blood rheology, platelet activation, and endothelial dysfunction predisposes to thrombosis and is the major underlying cause of access failure.

However, access stenosis is not the sole cause of thrombosis. Access thrombosis has been reported to occur without radiological evidence of a significant stenosis in up to 15% of grafts.[30] Studies using prospective flow monitoring have shown that access thrombosis occurs without a drop in blood flow rate suggestive of a hemodynamically significant stenosis.[87] Moreover, clinical observation also suggests that many episodes of thrombosis occur in the night often after a preceding dialysis session. This suggests that volume depletion post dialysis with the resulting hemoconcentration and low cardiac output may predispose to access thrombosis. Thus factors other than stenosis likely contribute to the high rate of thrombosis in grafts.[88]

A normal endothelial barrier is needed to regulate activation of coagulation pathways and prevent thrombosis.[89] Endothelial dysfunction is common in patients with kidney disease. Evidence for endothelial dysfunction, including decreased endothelial nitric oxide formation and increased circulating levels of various endothelial-derived proteins (e.g., von Willebrand factor, P-selectin, and plasminogen activator inhibitor, PAI-1), has been found in patients with kidney disease and may contribute to a generalized prothrombotic state contributing to graft thrombosis.[90,91] Increased wall tension within the venous limb of the graft may also lead to decreased thrombomodulin expression by endothelial cells and contribute to thrombosis.[92]

Endothelial dysfunction may contribute to the chronic activation of coagulation and fibrinolytic pathways seen in many patients with chronic kidney disease.[89] Circulating levels of tissue factor and factor VII activity are reportedly increased suggesting activation of the extrinsic pathway of coagulation while elevated levels of prothrombin activation fragments (F1+2) and thrombin-antithrombin complexes (TAT) suggest ongoing thrombin activation.[93,94] Elevated D-dimer levels have been reported suggesting increased activation of both the thrombotic and the fibrinolytic pathways.[94] Coagulation pathways are also activated by inflammatory stimuli[95] that frequently is present and fluctuates with time in people with renal failure.[23] Hence the risk for thrombosis likely will vary depending on inflammatory insults to the patient. Insertion of a vascular access graft itself induces an inflammatory stimulus [23] that may contribute to the enhanced risk of thrombosis compared to a autogenous fistula.

Platelet function has generally been shown to be impaired and contribute to the hemostatic (bleeding) defect seen in people with ESRD.[96] However, platelets are activated at the time of graft surgery and likely contribute to the very high rate of thrombosis immediately after access creation. Moreover, ongoing platelet activation by the high shear stress and abnormal luminal surface posed by the AV graft also contributes to graft thrombosis. Finally, hemodialysis has been shown to activate platelets and could further contribute to graft thrombosis.[96,97]

Other factors may contribute to a hypercoagulable state in people with ESRD.[88,89,96] The prevalence of antiphospholipid antibodies is increased in people on hemodialysis.[98] The lupus anticoagulant appears to be associated with a higher risk for thrombosis than anticardiolipin antibodies.[99] Antiphospholipid antibodies have been reported to be associated with hemodialysis access thrombosis in some studies[100] but not others.[98,101] A recent study suggested that the subset of antiphospholipid antibodies directed against protein C and protein S were elevated in hemodialysis patients and associated with access thrombosis.[102] Plasma homocysteine is also elevated in people with ESRD and is a modest risk factor for venous thrombosis.[103] However, lowering of homocysteine levels failed to reduce vascular access thrombosis in a recent trial.[104]

Infection

Infections and their complications account for about 11% of the annual mortality in ESRD patients.[24] Graft infection is a particularly serious complication that can be difficult to manage and has been an increasing cause of admission for hemodialysis patients.[24] Most studies report rates of graft infection between 5%-15% over the duration of the patency.[78,79] The risk of infection may be higher in the first year after access placement.[79] The majority of infections are due to *Staphylococcus aureus* and *S. epidermidis*.[105,106] Less commonly encountered organisms include Enterococcus, gram negative bacteria, and occasionally candida or other fungal species.[105,106] Infection or abscess around the access may present with localized erythema and tenderness over the site, but AVG infection can also present with fever and systemic symptoms without localized evidence of infection.[107] Tagged white blood cells or antigranulocyte antibody scans have been used to detect occult AVG infections.[107,108] Serious complications of access infection include thrombosis, metastatic seeding leading to endocarditis, osteomyelitis, marantic abscess, sepsis, and death. Nasal carriage of *Staphylococcus aureus* has been reported as a risk factor for access infection.[109] Other factors that predispose to graft infection include frequent access surgeries and procedures, poor personal hygiene, intravenous drug abuse, and skin rash or infection.[106] Careful attention to bactericidal cleansing of the skin and infection control practices at the time of needle insertion in the dialysis unit is a very important quality control measure. The use of preoperative vancomycin before the access surgery has been recommended to decrease the frequency of subsequent postoperative graft infections.[110]

Management of AVG infection typically requires excision of the infected graft material and treatment with antibiotics.[106,111] Vancomycin with addition of gram-negative coverage if the patient is septic is appropriate. However, long-term use of vancomycin should be avoided and alternate antibiotics chosen as soon as the results of antibiotic sensitivity testing are known. A strategy to limit vancomycin use consists of initiating therapy with a first generation

cephalosporin and an aminoglycoside until culture and sensitivity results are known and then adjusting the antibiotic regimen accordingly.[111] If alternate access sites are limited and the infection is localized outside the graft, local incision and drainage of the access site without removing the graft can be attempted.[106] An alternate strategy under investigation is to replace the infected graft with a biograft that is more resistant to infection.[112] If an endovascular source of infection is present, then it should be treated for 6 weeks with appropriate intravenous antibiotics to reduce the risk for late sequelae from metastatic seeding.

Access Stenosis

Pathophysiology Access stenosis is the underlying etiology for most access thrombosis and failure. The stenotic lesion at the venous anastomosis has been characterized pathologically as a dense neointimal hyperplasia.[113,114] Histochemically, the neointimal thickening consists predominantly of myofibroblasts with some smooth muscle cells along with associated extracellular matrix material.[115] Prominent capillary infiltration (angiogenesis) is found throughout the neointima and particularly at the intima media boundary. Macrophages are found lining the surface of the graft, infiltrating the graft matrix, in the adventitia of the vein and in association with capillaries in the neointima.[113,114] Immunohistochemical studies reveal that the neointima stains strongly for the smooth muscle mitogens PDGF, FGF, insulin like growth factor and endothelin, the matrix stimulating cytokine transforming growth factor-β, matrix modulating enzymes, and the endothelial mitogens VEGF and FGF.[113,114,116] Indices of increased oxidative stress have been reported within the neointima.[117] Increased cellular proliferation is present throughout the lesion in the neointima, media, and adventia.[114] In contrast to advanced atherosclerotic lesions, a lipid core and fibrous cap are not seen.

The pathophysiology leading to the venous neointimal hyperplasia in AVGs is not known but is assumed to involve some of the same processes, leading to neointimal hyperplasia seen after arterial injury.[113,114] The predominant localization of stenosis at the graft-vein anastomosis and in the immediate downstream vein suggests that mechanical injury at the time of surgery, the inflammatory reaction to the graft material, venous hypertension, increased turbulence, and altered wall shear stress may all be factors that contribute to neointimal hyperplasia.[114]

Monitoring to Detect Access Stenosis Longitudinal observational studies have reported that an active access surveillance program can decrease the rate of graft thrombosis and may increase overall access survival.[83,118] Based on these studies, the K/DOQI Guidelines recommended an organized approach to access monitoring/surveillance with regular assessment and tracking of access function to detect and treat access stenosis.[80] Several approaches are used for access surveillance (Table 21-5).[80] The optimal approach would have a high sensitivity and specificity for the detection of access stenosis at high risk of thrombosis and be easy to perform at each dialysis session and inexpensive. Currently no surveillance technique has been shown to meet all of these criteria.[118]

Clinical examination of the graft and downstream vein by an experienced observer can detect hemodynamically significant access stenosis particularly when it occurs at the venous anastomosis.[119,120] As shown in Table 21-6, the examination focuses on noting the presence and location of any palpable thrills, the character of the pulse, the presence of pulse augmentation with downstream venous occlusion, whether the venous limb of the access collapses with arm elevation, and the nature of the audible bruit. Development of significant swelling in the access arm suggests the presence of a central vein stenosis most likely from a prior central catheter or cardiac pacemaker. In the hands of an experienced examiner, a careful clinical exam reportedly has a positive predictive value of 88% to detect a hemodynamically significant stenosis at the vein-graft anastomosis but much lower in other regions of the access.[120] However, the practicality of this approach and the sensitivity and specificity of routine clinical exams to detect stenosis in the usual care setting has not been tested.

A variety of additional surveillance techniques based on hemodynamic measurements have evolved to detect the presence of access stenosis.[80] Development of a hemodynamically significant stenosis (>50%) leads to an increase in access resistance that can be detected by a drop in access blood flow rate (Qa) and an increase in intraaccess pressure (P_{IA}) upstream of the stenosis. When access blood flow drops below the dialyzer blood pump rate (typically 400 ml/min), recirculation

TABLE 21-5 Techniques for Access Monitoring/Surveillance to Detect Stenosis

Clinical exam
Access recirculation
Venous pressure
Dynamic pressure
Static pressure
Access flow rate
Direct visualization
Doppler ultrasound
Angiogram
Magnetic resonance angiography

TABLE 21-6 Results of Clinical Examination of the Graft and Downstream Vein

PARAMETER	NORMAL	STENOSIS*
Thrill	Only at arterial anastomosis	At site of stenotic lesion
Pulse	Soft, easily compressible	Water-hammer
Pulse augmentation†	Normal augmentation	Absent augmentation
Arm raise	Vein collapses	Vein remains distended upstream of stenosis
Bruit	Low pitched Continuous Diastolic and systolic	High pitched Discontinuous systolic only

*Abnormalities listed are for the two extremes: completely normal and severe stenosis. With lesser degrees of stenosis, the findings will be between these two extremes.
†Pulse augmentation is performed by noting the increase in pulse at the venous anastomosis that occurs after occluding the downstream vein.
(From G.A. Beathard, An algorithm for the physical examination of early fistula failure, Semin. Dial. 18 [2005] 331-335.)

will occur leading to a decrease in adequacy of dialysis (i.e., kT/V or urea reduction ratio [URR]. Each of these parameters (Qa, P_{IA}, and recirculation) has been used as a surveillance technique to detect the development of access stenosis.[80] Access blood flow (Qa) and recirculation can be measured by a variety of techniques based on the indicator-dilution method (i.e., Fick principle).[121] Intraaccess pressure (P_{IA}) is measured using a manometer connected to a needle inserted into the access. Blood flow through the needle must be zero (i.e., static flow).[122] Otherwise, if the measurement is made while blood is flowing through the needle during dialysis (e.g., dynamic venous drip chamber pressure, P_{DC}), then the measurement must be corrected for the drop in pressure across the needle and the height of the drip chamber above the access to get an accurate intraaccess pressure.[123] There are caveats to the use and interpretation of each of these three techniques.[124,125] Generally serial measurements over time are better than a single isolated measurement for the detection of stenosis.[126] Nevertheless, the sensitivity and specificity of all of the available techniques has been found to be suboptimal for routine surveillance of fistulas or grafts.[118]

In the absence of regular hemodynamic surveillance, routine clinical monitoring provides clues to the development of stenosis.[80] A progressive decrease in the adequacy of dialysis suggests the presence access recirculation. A progressive decrease in arterial drip chamber pressure or increase in venous drip chamber pressure suggests the presence of arterial or venous stenosis, respectively. Prolonged bleeding after dialysis may suggest a significant downstream venous stenosis while increased swelling of the access extremity suggests central venous stenosis. Although clinical monitoring is insensitive, it is readily available and should be used in conjunction with clinical examination of the access in a cost effective approach to access surveillance.

An alternative to hemodynamic measurements is direct visualization of the access by Duplex ultrasound, angiography, or magnetic resonance angiography (MRA).[127] Duplex ultrasound and MRA can also provide information on access flow rate. Several studies have documented the ability of routine Duplex ultrasound monitoring to detect access stenosis and decrease the rate of access thrombosis.[128,129] However, Duplex ultrasound requires specialized equipment and training and may not be practical for routine monitoring in most dialysis units. Similarly, the use of MRA or angiography is not practical or cost-effective to use for routine access screening. Gadolinium-enhanced MRA also carries the risk of nephrogenic systemic fibrosis in this population. Conventional angiography is useful to confirm the suspected stenosis and to plan the appropriate intervention.

There have been six randomized controlled trials looking at the efficacy of access surveillance using Qa, P_{IA}, or Duplex ultrasound in addition to routine access monitoring to reduce graft thrombosis and prolong graft patency.[118] Access surveillance increased the rate of angioplasty procedures in all studies where it was reported. However, in five of six studies, there was no improvement in either the rate of thrombosis or in overall graft survival.[118] Collectively, the studies to date do not support the use of additional access surveillance on top of routine clinical monitoring for grafts or fistulas.[54]

Treatment and Prevention of Graft Failure Graft stenosis in the absence of thrombosis can be treated by either surgical resection or percutaneous transluminal angioplasty. Depending on the site of the stenosis, surgical treatment may consist of an outflow patch graft to widen the venous anastomosis, resection, or bypass of the stenotic segment. Angioplasty has become the preferred method in most centers for the initial treatment of access stenosis because it can be done at the time of confirmatory angiography and it preserves vessels for future surgery.[130] The stenotic lesions are denser than typical atherosclerotic lesions and require a higher balloon pressure (up to 20 atm for at least 1 to 2 minutes) to achieve a satisfactory result (typically defined as <30% stenosis after angioplasty).[131] Restenosis occurs rapidly after angioplasty with a median patency of about 6 months.[81,130,131] Endovascular stents have not been shown to prolong the primary patency after angioplasty of graft stenosis.[132] However, stents may be useful in selected situations such as rapid recurrent restenosis, significant elastic recoil after angioplasty, or where surgical options are limited.[133] Endovascular stents are also frequently used to treat central venous stenosis where surgical options are limited.[53,134] However, repeated interventions are often necessary to maintain patency of the central veins. Endovascular stents have been used to treat access complications such as venous rupture after balloon angioplasty or pseudoaneurysms.

If access thrombosis has occurred, percutaneous thrombolysis or surgical thrombectomy is required to restore patency and should be followed by angiography or other imaging technique to detect and treat any underlying stenosis. A crossed-catheter pharmaco mechanical approach using a thrombolytic agent is most frequently used for percutaneous thrombolysis, but mechanical thrombolysis using saline has also been shown to be effective.[135] Percutaneous thrombolysis and surgical thrombectomy have been reported to be similarly effective at restoring short-term patency as long as stenotic regions are identified and treated.[136–138] For both approaches, restenosis after thrombosis occurs more rapidly (median patency about 90 days) than after angioplasty for stenosis without thrombosis.[31] Although repeated angioplasty can preserve access function temporarily, access patency tends to decline with each angioplasty.[81] Ultimately, surgical revision or placement of a new access is required in most people who suffer recurrent bouts of graft stenosis and thrombosis.[139]

Given the high costs and patient morbidity associated with treating graft stenosis and thrombosis, increasing attention has been directed to the primary prevention of these complications. Because thrombosis is the ultimate cause of access failure, treatment with anticoagulants and antiplatelet agents have been tried.[88] In uncontrolled trials, anticoagulation with warfarin or heparin has been reported to prolong access survival in people who have had frequent access thrombosis often in association with antiphospholipid antibodies.[140,141] In a small study of 16 people with anticardiolipin antibodies and recurrent thrombosis the use of warfarin (target INR of 2-3) produced a small but statistically significant increase in graft survival.[142] However a recent randomized controlled trial of low dose warfarin, targeting an INR of 1.4 to 1.9 found no benefit (and possible harm) of warfarin over placebo in preventing access thrombosis in subjects who received a new hemodialysis graft.[143] Use of anticoagulants should not be used as a general strategy to prevent graft thrombosis; however, in selected patients

with frequent graft thrombosis and a known prothrombotic condition, these agents can be considered if the benefit appears to outweigh the risk.

Antiplatelet agents have been reported to prevent arterial graft occlusion. In newly created hemodialysis grafts, a small study demonstrated that dipyridamole alone or in combination with aspirin decreased the risk of thrombosis compared to placebo.[144] Recently, the results of a randomized double-blind placebo-controlled trial in 649 patients was reported examining the effect of extended release dipyridamole (200 mg) plus aspirin (25 mg) (ERDP/ASA) given twice a day on primary unassisted graft patency in newly created grafts.[145] Treatment with ERDP/ASA produced a modest but statistically significant reduction in the risk of stenosis and increase in the duration of primary unassisted graft patency. The incidence of primary unassisted patency at 1 year was 23% in the placebo group and 28% in the ERDP/ASA group (5% absolute increase).[145] Of note, patients were allowed to participate even if they were on aspirin. In the subgroup of patients not on aspirin, ERDP/ASA produced a nearly 10% absolute improvement in primary unassisted patency at 1 year. Treatment was stopped at the loss of primary patency. There was no increased risk of bleeding or other adverse events and no effect was seen on cumulative patency or patient survival.

The Department of Veterans Affairs (VA) Cooperative Study Group also performed a randomized controlled trial looking at the combination of aspirin (325 mg per day) plus clopidogrel (75 mg per day) compared to placebo on graft thrombosis in 200 subjects with prevalent grafts.[146] The study was terminated early as a result of a twofold increased risk of bleeding in the treatment group without observing a significant benefit of active treatment to reduce graft thrombosis. However, the study did note a trend towards improved graft survival for active treatment in the subgroup of subjects who had never suffered an episode of graft thrombosis.[146]

Aspirin has also been noted to be associated with a decreased risk of graft thrombosis[147] and cumulative graft failure[148] in two recent prospective observational studies. However, the effect of aspirin on graft patency was not statistically significant in another.[149] Taken together, the results suggest that treatment with an antiplatelet agent at the time of graft creation will modestly prolong primary unassisted patency. Use of two antiplatelet agents may carry an unacceptable risk of bleeding in this population. The optimal antiplatelet agent to use, the cost effectiveness of this therapy, and the effect on cumulative graft patency remain to be determined.

Fish oil capsules containing omega-3 polyunsaturated fatty acids have been shown in several randomized controlled trials to reduce the risk of atherothrombotic events (i.e., recurrent myocardial infarction and death) in people who have known coronary artery disease.[150] A small pilot study of fish oil done in seven hemodialysis patients who had frequent recurrent graft thrombosis found no effect on graft thrombosis at 6 months.[151] Two small randomized, double-blind trials comparing the effect of fish oil to a corn oil control on graft thrombosis have reported mixed results.[152,153] A larger randomized trial of fish oil therapy is in progress.[154]

Several trials have looked at the effect of ionizing radiation in the form of either external beam irradiation or intravascular brachytherapy to prevent neointimal hyperplasia and graft failure.[155,156] Despite encouraging preclinical trials, clinical trials of radiation for AV stenosis have failed to prolong access patency.[155,156] New therapies are on the horizon that offer promise to prevent neointimal hyperplasia and prolong graft survival.[114] Autologous tissue grafts offer promise to avoid the inflammatory effect of prosthetic grafts or allogenic biografts.[71] Local therapy applied to the graft before implantation or at the vein-graft anastomosis at the time of graft surgery is a new approach that can limit systemic drug toxicity and allow a therapeutic agent to be focused at the major site of neointimal hyperplasia. Clinical trials of this approach include the use of an oligonucleotide E2F transcription, factor decoy applied to vein grafts (www.clinicalTrials.gov, #NCT00086164) and allogenic human endothelial cells applied in a Gelfoam matrix (Vascugel®) to the graft vein anastomosis (www.clinicalTrials.gov, #NCT00479180). Other local therapies applied either to the luminal or adventitial side of the vein-graft anastomosis are being considered,[114] but concerns regarding impaired healing and aneurysm formation leading to vein rupture will need to be monitored. Finally, in addition to graft design and pharmacological therapy, attention to details in surgical placement, graft cannulation, infection control practices, and maintenance of an access database to monitor outcomes are all aspects of routine care that are difficult to quantitate but are likely to contribute to prolonging access survival.

CENTRAL VENOUS CATHETERS

Despite guidelines recommending early placement of an AV access and limiting CVCs to no more than 10% of all prevalent accesses, currently 82% of patients in the United States start dialysis with a CVC and 19%-25% use a CVC as their permanent access.[24,25] CVC use has also been increasing in many other countries.

Catheter Design

Catheters used for hemodialysis must deliver high blood flow rates with minimal recirculation, be biocompatible, have low thrombogenicity, produce minimal damage to the vein wall, and resist infection. There has been steady evolution and progress in catheter design, but many challenges remain.[157]

Current catheters are made of silicone, polyurethanes or copolymers. Silicone is soft and flexible, making it less likely to damage vascular tissue, but requires a thicker wall to avoid lumen collapse and is weakened by exposure to iodine. Polyurethane is more rigid than silicone, allowing for thinner catheter walls, and is thermoplastic (i.e., more flexible when warmed to body temperature), making it easier to insert, particularly for acute hemodialysis. Polyurethanes are susceptible to alcohols (e.g., Mupirocin) but resistant to degradation by iodine or petroleum-based antibiotics (e.g., Neosporin®). Copolymers such as Carbothane® (polyurethane/polycarbonate copolymer) have the advantages of polyurethane but are stronger, less susceptible to chemical degradation and are increasingly being used for dialysis catheters. To assist in radiographic visualization, a small amount of radio opaque material (e.g., barium) is added to

the catheter in manufacturing. Catheters are also available with a variety of surface coatings designed to reduce infection or thrombosis.

Catheter design focuses on three main areas: the external segment of the catheter after it exits the vein, the catheter shaft, and the distal end containing the ports for blood entry and exit. The external limb of the catheter can either be tunneled under the skin or not. Non tunneled catheters are typically used for acute hemodialysis. Tunneled catheters, often with a subcutaneous Dacron or plastic cuff, are typically reserved for chronic (>2–3 weeks) hemodialysis access. The catheter shaft is designed to balance competing goals of maximizing blood flow rate yet minimizing external diameter and catheter rigidity to limit vein trauma. The most efficient shaft design for dual lumen catheters is the double D. Most current dual lumen hemodialysis catheters range from 12F-16F with larger sizes being used for tunneled chronic catheters. Current tunneled catheters can accommodate blood flow rates of 300–400 ml/min or more at a pressure of 200 mmHg.[158] The greatest variation in catheter design occurs at the distal end in an effort to optimize flow rate, minimize recirculation and reduce clotting to extend long-term catheter patency. Variations in catheter design have been reviewed by Ash.[157] Although several clinical studies of different catheter designs have been published, there is no consensus as to which design is the best.[158]

TABLE 21-7 Catheter Complications[159,160,162]

Acute Complications (Placement)
Any site
External bleeding, perivascular hematoma
Arterial puncture
Arterial dissection/occlusion
Air embolism (subclavian and jugular >femoral)
Local nerve injury
Femoral vein
Retroperitoneal hemorrhage
Subclavian or jugular vein
Pneumothorax
Mediastinal or pleural hemorrhage
Atrial puncture and pericardial hemorrhage
Arrhythmias
Chronic complications
Infection (blood stream, subcutaneous exit site)
Thrombosis, pulmonary embolus
Fibrin sheath formation
Vein stenosis
Arteriovenous fistula formation

Advantages and Disadvantages

Catheters offer some advantages but also significant risks compared to an AV access.[159] Catheters provide rapid access to the circulation when an AV access is not present and can be placed in most patients in a number of different locations. They do not cause vascular steal, heart failure, or pulmonary hypertension and are easy to use for hemodialysis. They also can be readily replaced when they fail or are infected. However, catheters carry significant risks including blood stream and exit site infections, thrombosis, central vein stenosis, and inadequate dialysis. Catheters also incite a chronic inflammatory stimulus. CVCs are associated with more hospitalizations, greater morbidity and mortality, and higher overall annual per person costs than an AV access.[14,15,20,24]

Indications

Catheters are primarily indicated as a temporary access for treatment of acute renal failure or as a bridge to a permanent AV access in patients needing chronic hemodialysis. Catheters may be indicated as a permanent access for the rare patient who has exhausted all other vascular access options. Catheters should not be used as a permanent access in patients waiting for a deceased donor kidney transplant as this could take many years.

Acute Hemodialysis Catheter Management

Dual-lumen, noncuffed temporary catheters are best suited for short-term acute hemodialysis, particularly in the unstable or septic patient.[160] These catheters are rigid at room temperature, thus aiding insertion, but become pliable when they achieve body temperature after insertion. The risk of infection or dysfunction is greater but these catheters are more easily replaced than a tunneled catheter.

Acute dialysis catheters may be placed in one of three main anatomical locations: the femoral, jugular, or subclavian vein. Femoral vein catheterization has the lowest risk of acute life-threatening complications. However, the patient must remain lying down while the catheter is in place. Using femoral catheters 19–20 cm long avoids recirculation seen with shorter catheters.[161] Jugular and subclavian catheters allow more freedom of movement and are more suitable for chronic use; however, they carry greater risk associated with intrathoracic bleeding or air entry (Table 21-7).[162] Central vein stenosis, a late complication, occurs more often with subclavian than with jugular insertions and is higher with left-sided than right-sided jugular catheters.[82] Thus cannulation of the subclavian vein for hemodialysis should be avoided in patients who may need future AV access placement for ESRD.

All percutaneous catheterizations carry the acute risk of external bleeding, perivascular hematoma formation, arterial puncture, and air embolism (see Table 21-7).[162] Arterial dissection and occlusion, AV fistula formation, and local nerve damage can also occur. Femoral catheters carry the risk of retroperitoneal hemorrhage, whereas subclavian and jugular catheters can result in pneumothorax, mediastinal, pleural, or pericardial hemorrhage.[159,160] Use of real-time ultrasound guidance for catheter insertion is strongly recommended.[163] Real-time ultrasound increases the success rate and decreases the time for insertion and the rate of complications including catheter-related blood stream infections (BSIs).[163] Ultrasound is used before the procedure to localize the position of the vein and artery and exclude intramural thrombus. Use of real-time ultrasound

while cannulating the vein further enhances successful cannulation and reduces the incidence of inadvertent arterial cannulation.

Air embolism is a concern particularly when inserting jugular or subclavian catheters.[159,160] For jugular and subclavian catheters, patients should be maintained in the Trendelenburg position until the catheter is fully inserted and the blood lines occluded from air entry. Perforation of the great veins, another complication of catheter insertion, may be increased in patients who have previously had multiple line insertions and have developed central vein stenosis. Following placement of a jugular or subclavian catheter and before initiation of hemodialysis, it is imperative that a chest radiograph be obtained both to exclude a pneumothorax and confirm appropriate catheter position. If there is any doubt that the tip of the catheter is not within the great vessels, a vascular study should be performed by injecting a small amount of contrast into the catheter under fluoroscopic control.

Introduction of infection is a major concern with all central catheter insertions.[159,160] Migration of skin organisms along the catheter tract is the most common source of infection. Strict adherence to aseptic technique in placement and care of the catheter is crucial.[164] Chlorhexidine gluconate is the currently preferred skin antiseptic agent,[165] and chlorhexidine impregnated dressings have been shown to reduce catheter-related infections.[164,166] CVCs impregnated with chlorhexidine-silver sulfadiazine or minocycline-rifampin have also been shown to reduce the risk of acute catheter-related infections.[167] However, the risk of developing bacterial resistance with long-term use is unknown. Insertion of a preformed curved rather than a straight jugular catheter has been reported to reduce the rate of infectious complications.[168]

Femoral vein catheters have been reported to have a higher risk of infectious and thrombotic complications than jugular or subclavian catheters.[169,170] However, a recent large randomized controlled trial found no significant difference in infectious or thrombotic complications for acute hemodialysis catheters placed in the femoral or jugular vein.[170] Notably, there was a significant correlation between infection risk and increased BMI for femoral but not jugular vein catheters, suggesting that the femoral vein be avoided in morbidly obese patients.[170] In addition, the hazard rate of developing catheter colonization appeared constant over the time of observation (about 3 weeks), implying that there was no set time at which the acute catheter should be removed. This observation supports the CDC recommendations against scheduled replacement of CVCs.[171]

Development of bacteremia, sepsis syndrome, or an otherwise unexplained fever should prompt removal of the temporary dialysis catheter and replacement if needed, preferably 1–2 days after initiation of appropriate antibiotic treatment.[172–175] The gram-positive organisms, *S. epidermidis* and *S. aureus*, are the most frequent pathogens. However, gram-negative organisms are common and fungemia may also occur. Blood cultures should be obtained and initial treatment based on local antibiotic sensitivity profiles. Typically, vancomycin (10–20 mg/kg; up to a maximum dose of 2 g) is given initially. In critically ill patients, addition of gram-negative and possibly antifungal coverage may also be indicated. The culture results should guide antibiotic therapy once they are available. Typical treatment for culture positive bacteremia or candidemia is 2–3 weeks.[172–175] Infection with *S. epidermidis* may be treated for 5–7 days, whereas *S. aureus* should be treated for longer, typically 3 weeks.[172,175,176] Uremic patients who develop *S. aureus* bacteremia have a relatively high incidence of metastatic complications; these patients may develop infectious endocarditis, septic arthritis, osteomyelitis, or epidural abscess.[176] Patients who develop a metastatic focus of infection should have any accumulation of pus drained and should be treated for up to 6 weeks with parenteral antibiotics.

Chronic Catheter Maintenance

Tunneled cuffed catheters (TCC) are preferred for patients requiring long-term hemodialysis extending beyond 2–3 weeks.[159] TCC deliver higher blood flow rates with a lower risk of infection and are more convenient for patients than acute hemodialysis catheters. However, they take longer to insert and are often placed under fluoroscopy to assure proper placement with the arterial port of the catheter at the entrance to the right atrium.[158] Complications of TCC placement are similar to acute catheters as shown in Table 21-7. TCC are more flexible than acute dialysis catheters. Originally TCCs were inserted into the vessel using a rigid external sheath (split sheath) to facilitate catheter placement. However, an over-the-wire technique has been developed and gained favor.[158] Median cumulative TCC survival reportedly varies from 25%-80% at 1 year.[158,159,177] The most common reasons for removal are infection and irreversible catheter dysfunction commonly due to thrombosis or formation of a fibrin sheath.

Current TCCs can deliver blood flows of 400 ml/min at acceptable pump pressures. Impaired catheter flow may lead to insufficient dialysis. Criteria for catheter dysfunction include: an inability to achieve 300 ml/min blood pump flow rate (BPFR), a prepump arterial pressure (PPAP) <-250 mmHg or venous pressure >250 mmHg, a conductance (i.e., BPFR/PPAP) < 1.2, progressive decrease in URR below 65% (or kT/V < 1.2) or trouble aspirating and returning blood in the catheter.[80,178] Catheter blood flow rate between 200–300 ml/min may still provide adequate clearance (URR>65%) for many patients.[179] Evidence of inadequate clearance should be checked in these patients before embarking on further investigation or treatment.[173] However, a trend indicating progressively impaired function should be investigated.

Catheter dysfunction occurring within the first 1–2 weeks after placement that cannot be resolved (e.g., by repositioning the patient and flushing the catheter lumens) suggests a technical or mechanical problem (e.g., kinked catheter). If persistent or severe, this requires radiological evaluation.

Delayed catheter dysfunction is most often due to the presence of thrombus or an external fibrin sheath. This can be treated by intracatheter thrombolysis.[180] The most convenient agent currently available in the United States for catheters is recombinant tissue plasminogen activator (t-PA, e.g., alteplase). Typically, 1–2 mg of t-PA (1 mg/ml) is infused into each lumen and allowed to dwell for 30–60 minutes before assessing catheter function.[180] A second treatment can be administered or a prolonged dwell time of

24–48 hours can be used if the first dose is unsuccessful. Complications are reportedly low. Restoration of function is expected in 70%-90% of cases but median patency is typically 2–4 weeks only. Recurrent dysfunction requires radiological evaluation. The most common cause of persistent dysfunction is a fibrin (or more accurately a fibrocellular) sheath around the catheter.[181] It can be diagnosed by injecting a small dose of contrast into the catheter looking for contrast tracking up the sheath.[182] Catheter stripping has been used to remove the sheath.[183] However, the current preference is for balloon dilation of the catheter track to disrupt any external fibrin sheath before reinsertion of a new TCC.[181] The latter approach has been reported to yield a median catheter patency of over 1 year.[184] New catheter designs have been envisioned to combat the problem of fibrin sheaths.[158]

Thrombosis is a major cause of TCC failure.[159,177] Currently unfractionated heparin is the standard catheter locking solution to prevent thrombosis. Various citrate solutions (4%-47%) have also been studied as an alternative to heparin.[185,186] Four percent citrate appears to be equivalent to heparin but potentially less expensive.[187] The FDA does not approve the use of higher concentrations of citrate in the United States. Low fixed dose (1 mg) oral warfarin did not improve TCC survival.[188] Warfarin targeting an INR goal of 1.5–2.5 appears to decrease the risk of thrombosis but is not advocated for routine use because of the risk of bleeding.[189] The current recommendation for prevention of TCC thrombosis is to use either heparin (1000 units/ml) or 4% citrate at a volume just sufficient to fill the catheter lumen.[190]

Infection is the major cause of catheter failure and catheter-related morbidity and mortality. TCC infections can involve the exit site, the subcutaneous tunnel, or the blood stream.[191] Catheter-related BSI is the most feared complication of TCC, carrying the potential for endocarditis, metastatic infection and septic shock. The spectrum of microbial pathogens is the same as that for acute catheters listed previously. Reported rates of TCC-related bacteremia generally range between 1.6–5.5 episodes per 1000 catheter days.[173,192]

Consistent application of NKF-K/DOQI guidelines for TCC care has been reported to achieve bacteremia rates of 1.3/1000 days.[193] This includes washing hands and wearing gloves before working with the catheter, using a sterile drape, carefully disinfecting the caps and hub of the catheter, and using a face mask for both patient and dialysis technician during catheter connection and disconnection.[164,193] Regular attention to cleaning the exit site and changing the catheter dressing is important to reduce the incidence of exit site infections. Ongoing reeducation and assessment is required to maintain optimal infection control practices.

Many trials have now looked at using antimicrobials instilled either into the catheter lumen (i.e., catheter "locks") or applied to the catheter exit site to reduce the risk of catheter infection (Table 21-8).[192] Meta analysis of these trials has shown that both catheter locks and exit site treatments are very effective at reducing the risk of both bacteremia and exit site infections.[192] Collectively catheter locks reduce the rate ratio for bacteremia by 67% and for exit site infections by 33%, whereas exit site treatments reduced the rate of bacteremia and exit site infections by 79% and 78%, respectively. Risks were reportedly low, but ear and vestibular toxicity can occur with aminoglycosides and symptomatic, and usually transient hypocalcemia can occur using citrate. The studies were all less than 1-year duration and the risk of developing resistant organisms with long-term and widespread usage is unknown. Current NKF K/DOQI guidelines recommend cleaning the exit site with chlorhexidine or povidone-iodine but do not recommend use of prophylactic antimicrobial locks.

TABLE 21-8 Antimicrobial Catheter Locks and Exit Site Therapies Tested in Randomized Controlled Trials[192]

Antimicrobial Locks
Sodium citrate (various concentrations: 4%-46.7%)
Gentamicin (4-40 mg/ml) with or without citrate (3%-46.7%) or heparin
Taurolidine-citrate (1.35% taurolidine-4% citrate)
Minocycline (3 mg/ml) + EDTA (30 mg/ml)
Vancomycin (25 mg/ml) + gentamicin (40 mg/ml) + heparin
Cefazolin (10 mg/ml) + gentamicin (5 mg/ml) + heparin
Cefotaxime (10 mg/ml) + heparin
Topical exit site treatment
10% Povidone-iodine ointment
2% Mupirocin ointment
Polysporin ointment
Medihoney
Manuka honey

Exit site infections (ESI) can typically be treated with topical antibiotics without the need for catheter replacement.[172,193] If the ESI is slow to resolve, systemic antibiotics may be needed. Development of fever, chills, or unexplained hypotension in a patient with a CVC suggests a BSI. An evidence-based approach to the treatment of BSI in patients with a long-term catheter or implanted port is shown in Figure 21-6.[172] Blood cultures should be drawn from both the catheter and a peripheral site if possible. For a probable BSI, treatment is begun with empiric IV antibiotics, as discussed previously for acute hemodialysis catheters. If the patient is hemodynamically stable and there is no exit site or tunnel infection or metastatic foci of infection (i.e., an uncomplicated infection), a BSI as a result of coagulase-negative staphylococcus, and possibly enterococcus may be treated with appropriate systemic antibiotics and catheter lock solution without catheter removal.[172,173,193,194] However, if the fever persists or blood cultures remain positive, then the catheter must be replaced. For complicated BSI or infections as a result of other organisms (e.g., *S. Aureus*, *Pseudomonas* species or *Candida*), the long-term catheter should be removed and the patient treated with systemic antibiotics. The duration of IV antibiotics depends on the organism and systemic complications (Figure 21-6). Dialysis can be achieved using a short-term catheter until blood cultures are negative then a new TCC can be inserted. Follow-up surveillance blood cultures 1–2 week after antibiotics are completed is recommended. Use of a team approach with an access infection control manager may improve patient outcomes.[195]

A full list of references are available at www.expertconsult.com.

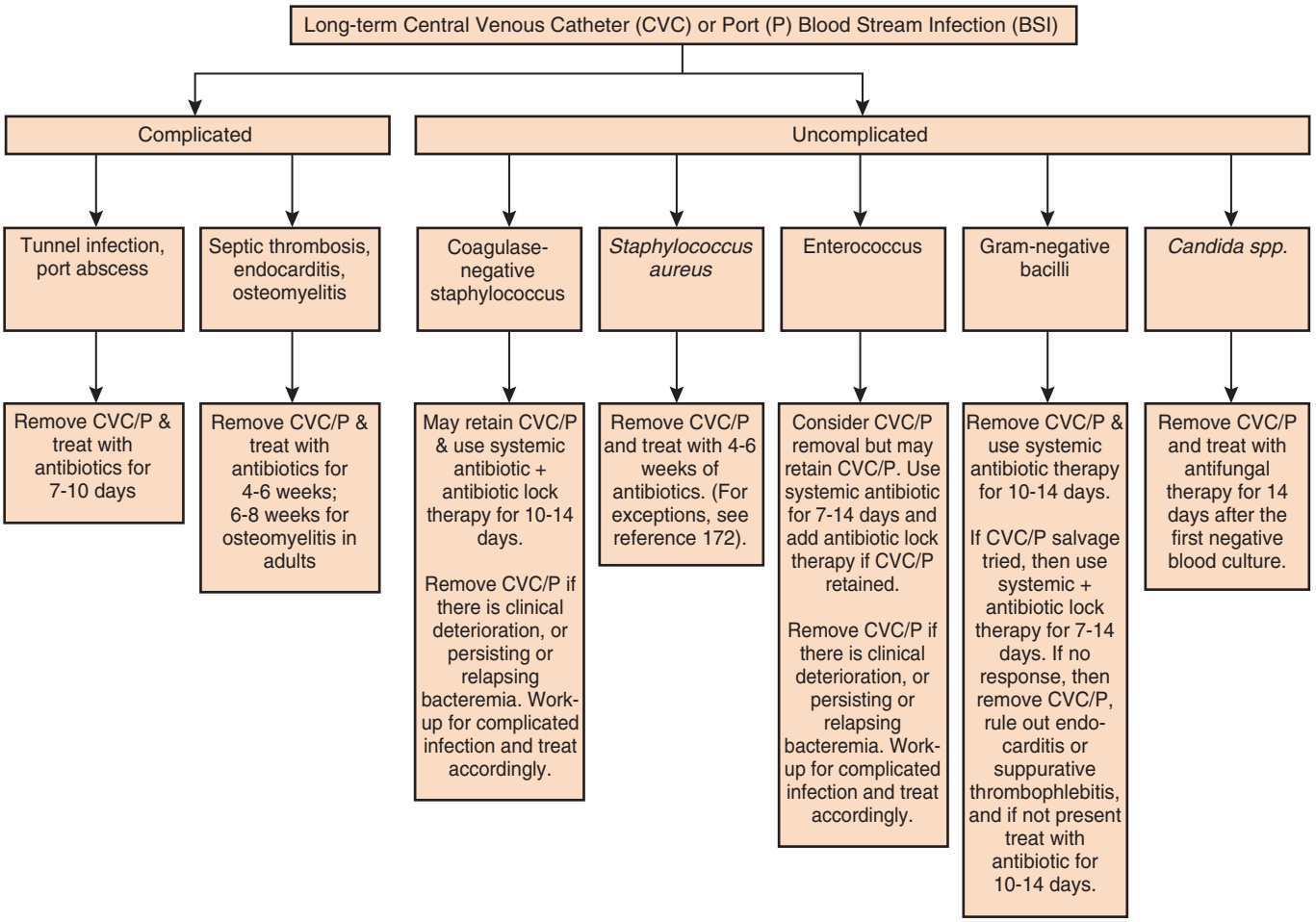


FIGURE 21-6 Algorithm to manage blood stream infections (BSI) in patients with a long-term central venous catheter (CVC) or implanted port (P). (Adapted with permission from L.A. Mermel, M. Allon, E. Bouza, et al., Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America, Clin. Infect. Dis. 49 [2009] 1-45.)

Chapter 22

HEMODIALYSIS ADEQUACY

John K. Leypoldt, Ph.D., Bruce F. Culleton, M.D., F.R.C.P.C. and Alfred K. Cheung, M.D.

UREMIC SYNDROME

Hemodialysis provides successful life-sustaining therapy for patients with limited or no kidney function. Many chronic hemodialysis patients have survived for more than 10 years of therapy, some for more than 30 years.[1,2] Despite this success in treating the uremic syndrome of end-stage renal disease (ESRD) patients by hemodialysis, knowledge of the toxins retained in the body after the loss of kidney function, so-called uremic toxins, and how much of those toxins to remove during hemodialysis therapy remains incomplete.

The uremic syndrome is a complex of multiple organ dysfunction resulting from the retention of molecules that are normally cleared by the kidneys; the number and types of such molecules are large.[3,4] Recent work suggests that more than 1000 different polypeptides with molecular weights greater than 800 daltons can be recognized in ultrafiltrate from patients on dialysis.[5] Such complexity would be challenging for the application of a therapy that attempts to specifically remove all uremic toxins and retain the beneficial solutes. In contrast, the approach using membranes to remove toxins based on a nonselective physical property, such as molecular size, has proven far more practical. Over the past 40 years, hemodialysis membranes have evolved from those that have small pores and only allow the passage of small uremic toxins, so-called low-flux hemodialysis membranes, to those that have larger pores that also permit the passage of larger uremic toxins, so-called high-flux hemodialysis membranes.[6] To simplify the types of uremic toxins to be removed during dialysis therapy, the European Uremic Toxin Work Group (EUTox) has classified these toxins into three main categories:[4] 1) low molecular weight water-soluble solutes; 2) molecules defined as middle molecules, that is, those with molecular weights greater than 500 daltons; and 3) low molecular weight solutes that are protein-bound. In addition to these toxins, the EUTox group has also identified inorganic ions such as phosphate as uremic toxins. This categorization of uremic toxins is helpful in understanding the relationship between the hemodialysis prescription and the dose of toxin clearance or removal.

In this discussion, hemodialysis therapy refers to three-times-per-week or thrice weekly treatments unless stated otherwise. The effect of more frequent hemodialysis treatment schedules will be described below in a separate section.

HEMODIALYSIS ADEQUACY

The term *adequacy* is used differently in the hemodialysis literature than in common usage. From a medical perspective, the term *adequacy* gives the impression that hemodialysis therapy adequately normalizes the patient body fluids or the internal milieu; however, this is not possible with current hemodialysis technologies. Instead, adequacy is used in the hemodialysis literature to define the treatment parameters that yield the best patient outcome in the context of the

conventional thrice-weekly hemodialysis schedule. This situation is akin to the optimization of a manufacturing process to achieve the most reproducible and best performing products (process optimization in the engineering literature). Stated in other words, hemodialysis adequacy refers to treating patients optimally given current resources. It is only when hemodialysis treatment schedules can be altered dramatically, as discussed later in this chapter, can the term *"adequacy"* be used in a medical context more generally.

In this chapter, the discussion of hemodialysis adequacy will focus on prescription parameters that alter uremic toxin removal during the hemodialysis treatment. These parameters will be confined to those that have been evaluated for effects on or associated with patient mortality, rate of hospital admissions, or patient quality of life. More limited discussion of other surrogate clinical endpoints, for example left ventricular hypertrophy, will also be discussed. In addition to uremic toxins, the removal of sufficient amounts of fluid and sodium is also paramount in defining adequacy of hemodialysis therapy. This topic, however, will not be discussed extensively in this chapter; the current discussion will be limited to the influence of the hemodialysis prescription parameters of treatment time and treatment frequency in relationship to adequate fluid removal.

The EUTox categorization of uremic toxins, outlined previously, can be used to facilitate the understanding of the relationship between certain hemodialysis prescription parameters and uremic toxin clearance or removal. The dose of uremic toxin clearance can accordingly be divided into three respective categories: 1) dose of low molecular weight water-soluble toxin clearance, 2) dose of middle molecule clearance, and 3) dose of low molecular weight protein-bound toxin (protein-bound molecules) clearance. It is useful to identify a marker solute for each category of uremic toxins. The dose of low molecular weight water-soluble toxin clearance is readily identified with urea and its commonly used dose parameter urea Kt/V (see later text). The clearance for such solutes during hemodialysis is high compared to that of the native kidneys and is limited primarily by the blood flow rate to the dialyzer and, to a lesser extent, by the dialysate flow rate and the surface area of the hemodialysis membrane. The most common marker solute for middle molecules is β_2-microglobulin, and the dose of middle molecule clearance is proportional to both the membrane surface area and the pore size of the membrane. Thus, middle molecules are removed to a significant extent during high-flux, but not low-flux, hemodialysis (see later text). Both urea and β_2-microglobulin can be readily measured in patient serum, and urea is commonly measured in clinical conditions. Clearance of protein-bound substances is more difficult to quantify; the most common marker solute used for categorizing protein-bound toxin clearance is *p*-cresol or *p*-cresol sulfate. It is important to note that the clearance of protein-bound toxins from the body relative to urea is not limited by the dialysis membrane pore size, but rather by biochemical or physiological resistances to removal of the bound toxin. Because the relationship between protein-bound solute clearance and patient outcome is only beginning to be understood,[7,8] and how to practically alter the clearance of these solutes during hemodialysis treatments remains poorly defined,[9,10] this specific class of uremic toxins will not be considered further in this chapter. Unless specified otherwise, the term *"small solutes"* will refer to low molecular weight water-soluble toxins only, not to those that are protein-bound.

RANDOMIZED, CONTROLLED CLINICAL TRIALS OF HEMODIALYSIS ADEQUACY

Three randomized, controlled clinical trials evaluating the adequacy of hemodialysis therapy, with appropriate statistical power to detect changes in mortality or hospitalization rates, have been completed to date. These were the National Cooperative Dialysis Study (NCDS), the Hemodialysis Study, and the Membrane Permeability Outcome (MPO) Study. The first two studies evaluated the effect of enhanced clearance of both low molecular weight water-soluble toxins (small solutes) and middle molecules; these studies differed in the interventions used to alter the clearance of the two categories of solutes. The latter study evaluated only the effect of enhanced clearance of middle molecules. The basic design and the primary outcomes of these studies are important because they provide level A or grade A evidence for supporting therapy guidelines.

National Cooperative Dialysis Study

The NCDS study was performed during the 1970s. It was a randomized clinical trial to assess hemodialysis treatment characteristics on clinical outcomes.[11] This interventional trial was designed to evaluate the effect of two prescription parameters thought to be critical determinants of hemodialysis adequacy:

1. Time-averaged concentration (TAC) of urea, as indicated by blood urea nitrogen (BUN), a marker inversely related to small solute clearance
2. Length of each hemodialysis session, or treatment time, as a surrogate for the clearance of middle molecules

The use of dialysis treatment time as a surrogate for middle molecule clearance in this study was an approximation because the removal of large, less readily diffusible solutes is primarily a function of the duration of dialysis, but also depends on hemodialysis membrane surface area.[12] Further, although it is often quoted that treatment time was used in this study as a surrogate for middle molecule clearance, Wineman[13] has alternatively suggested that treatment time was selected to assess its importance as a practical hemodialysis prescription parameter. The NCDS was not statistically powered to evaluate patient mortality as the primary outcome; instead, the primary outcome was the number of hospitalizations or mortality in each treatment arm.

In the NCDS, the measure used for quantification and targeting of urea clearance was the time-averaged BUN concentration over a full weekly dialysis cycle (TAC_{urea}). This measure assumes that the toxicity of small solutes during ESRD is more likely a function of the average toxin exposure than the predialysis BUN concentration. All patients in this study underwent rigorous and repeated kinetic modeling to achieve the specified TAC_{urea} for their assigned group.[14–16] The final study population consisted of 165 patients, randomized into four different intervention groups in a 2 × 2 factorial design, with all patient groups receiving

hemodialysis thrice weekly. Groups I and III were treated to achieve a TAC_{urea} of 50 mg/dl, whereas Groups II and IV were treated to achieve a TAC_{urea} of 100 mg/dl. Groups I and II were assigned the longer treatment times, 4.5 to 5 hours, whereas Groups III and IV had treatment times of 2.5 to 3.5 hours. The designated TAC_{urea} was achieved by altering the blood and dialysate flow rates and membrane surface area of the dialyzers. The randomized intervention was for 24 weeks.

TAC_{urea} was found to be the most important determinant of patient morbidity during the study or withdrawal from this study.[11,17,18] The proportions of patients not withdrawn for medical reasons or death by 9 months were 89% and 94% for the low TAC_{urea} groups (I and III) versus 55% and 54% for the high TAC_{urea} groups (II and IV). The effect of dialysis treatment time was not considered statistically significant ($p = 0.06$). TAC_{urea} was also a highly significant determinant of the rate of hospitalization, with fewer hospitalization admissions occurring in the low TAC_{urea} groups. Further, Group I patients had fewer hospitalizations than Group III; similarly, and Group II had fewer hospitalizations than Group IV. In contrast, the effect of treatment time on hospitalization was statistically significant in the high TAC_{urea} groups only, with longer treatment time (Group II) being associated with lower risks than shorter treatment time Group IV).[17]

A stepwise, linear logistic regression analysis of the data from the NCDS was performed to determine the effect of multiple treatment variables on the probability of an adverse outcome.[18] Subsequent death, withdrawal from the study or hospitalization during the first 24 weeks of follow-up was again predicted by TAC_{urea}. The second best predictor of patient outcome was the protein catabolic rate (PCR),[11,17,18] also called the protein nitrogen appearance rate, an approximation of the dietary protein intake in dialysis patients at steady state. In a subsequent mechanistic analysis of the data from the NCDS, however, it was argued that this statistical association was a consequence of the protocol design (i.e., the PCR was not an independent variable).[19] This lack of independence is most evident when one appreciates that, to achieve a predetermined TAC_{urea}, the amount of hemodialysis prescribed must be a function of the PCR. Thus, a higher PCR requires a greater amount of dialysis to achieve the same TAC_{urea}, and vice versa. Hence any statistical correlation between TAC_{urea} and clinical outcomes will be mirrored by PCR. The design of the NCDS did not set PCR as a study variable. For all study groups, the PCR was permitted to fluctuate widely between 0.8 and 1.4 g/kg/day.

It is apparent from the NCDS results that urea is an appropriate surrogate small solute marker and that the level of urea clearance or removal predicts patient outcomes. However, several design limitations compromised the applicability of this study to the current ESRD patient population and modern treatment practices. For example, the NCDS excluded older patients (>60 years of age) and diabetic patients; these patient profiles would exclude the preponderance of current Americans with ESRD.[20] Further, the dose of dialysis as assessed by urea Kt/V (see below) was considerably lower in the NCDS than in the 21st century; approximately half of the patients in the NCDS were treated with a single-pool urea Kt/V of less than 0.8.[19] Furthermore, participants in the NCDS were treated exclusively with low-flux cellulosic hemodialysis membranes that had clearances for middle molecules that would be considered negligibly small by modern standards. Finally, the follow-up period for the NCDS was 48 weeks or less and therefore did not adequately address more fundamental long-term outcomes, such as mortality. Despite these limitations, the NCDS is the foundation for the use of urea as a surrogate low molecular weight uremic toxin in the measurement of hemodialysis adequacy.

The Mechanistic Analysis of the National Cooperative Dialysis Study

One of the most significant findings from the NCDS was the subsequent mechanistic analysis of this trial by Gotch and Sargent.[19] It was readily known before and during this trial that the parameter urea Kt/V was instrumental in regulating and monitoring BUN concentrations; however, the mechanistic analysis was the first description of the use of this parameter to evaluate patient outcomes. The interpretation of the NCDS using the statistical model[17,18] was that the optimal therapy prescription would be comprised of high protein intake and intensive dialysis. In contrast, the mechanistic analysis indicated that a fully adequate hemodialysis prescription was provided by a PCR of 1 g/kg body weight and a single-pool urea Kt/V of 1 and that any additional protein intake or dialysis would be of no apparent clinical value.[19] This interpretation of the NCDS had a profound impact on the international dialysis community, such that urea Kt/V has been considered the gold standard measure of the dose of dialysis, even though it quantifies small solute clearances only. The significance of this interpretation of the NCDS results cannot be overstated; it implies that the product of average urea clearance across the dialyzer (K) and treatment time (t) divided by the urea volume of distribution in the body (V) for a given patient, or urea Kt/V, alone determines the adequacy of hemodialysis therapy. Thus, urea Kt/V as an expression of the dose of small solute clearance will be discussed in greater detail below. Although this construct for evaluating the dose of small solute clearance has enjoyed almost universal acceptance for approximately two decades, it should be noted that the mechanistic analysis was an *"as-treated"* analysis not the *"intent-to-treat"* analysis that is now universally applied to randomized clinical trials. There has been increasing concern of the adequacy of using this parameter alone as a guide to dialysis.

Hemodialysis Study

The Hemodialysis (HEMO) Study was a prospective, randomized, multicenter clinical trial designed to study the effects of the dose of small solute clearance (defined in this trial as *"dialysis dose"*) and membrane flux on hemodialysis patient morbidity and mortality. Patients were randomized using a 2 × 2 factorial design to target equilibrated Kt/V (eKt/V, see later text) of either 1.05 or 1.45 and to the use of either a low-flux or a high-flux membrane dialyzer. The definition of low-flux and high-flux membranes used in the randomized groups was based on both dialyzer membrane ultrafiltration coefficient and dialyzer clearance of β_2-microglobulin.[21] Entry criteria of the study included a thrice weekly treatment schedule, ages between 18 and 80 years, residual kidney urea clearance less than 1.5 ml/min/35 L of

urea distribution volume in the body, and anticipated ability to achieve a target eKt/V of 1.45 within a 4.5-hour hemodialysis session. Between 1995 and 2001, 1846 patients were randomized in 72 dialysis units affiliated with 15 clinical centers in the United States. More details on the study design and implementation have been reported elsewhere.[22]

Patients randomized to the standard-dose group were treated for 190 ± 23 (mean ± SD) minutes and achieved a delivered single-pool Kt/V (spKt/V) of 1.32 ± 0.09 and a delivered equilibrated (eKt/V) of 1.16 ± 0.08, whereas those randomized to the high-dose group were treated for 219 ± 23 minutes and achieved a spKt/V of 1.71 ± 0.11 and a delivered eKt/V of 1.53 ± 0.09. No differences in β_2-microglobulin clearance between the standard-dose and high-dose groups were noted. Similarly, there were no differences in dialysis dose parameters between the low-flux and high-flux groups, although β_2-microglobulin clearance was 3.4 ± 7.2 ml/min for the low-flux group and 33.8 ± 11.4 ml/min for the high-flux group.

The primary analysis for the HEMO Study demonstrated no significant difference in all-cause mortality between patients treated in the standard-dose and the high-dose groups and between those in the low-flux and high-flux groups.[23] Kaplan-Meier survival curves for the dose and flux interventions are shown in Figure 22-1. There were also no

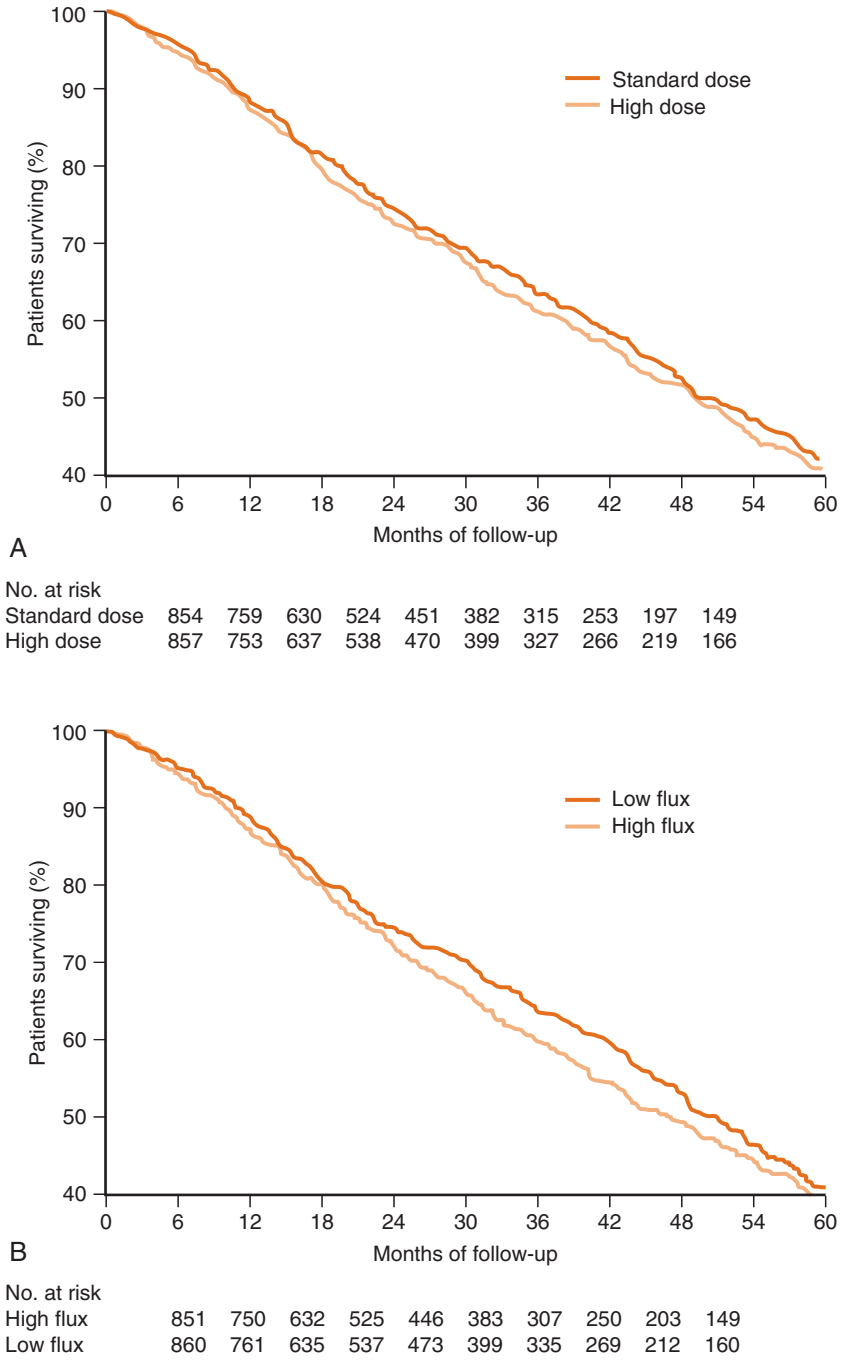


FIGURE 22-1 Kaplan-Meier survival curves for the randomized dose **(A)** and flux **(B)** interventions in the Hemodialysis (HEMO) Study. The curves are adjusted for multiple baseline factors. All-cause mortality in the high-dose group was 4% lower ($p = 0.53$) than that in the low-dose group, and all-cause mortality in the high-flux group was 8% lower ($p = 0.23$) than that in the low-flux group. (Reproduced with permission from G. Eknoyan, G.J. Beck, A.K. Cheung, et al., Effect of dialysis dose and membrane flux in maintenance hemodialysis, N. Engl. J. Med. 347 [2002] 2010-2019.)

significant differences between the treatment arms in the secondary composite outcomes of all-cause mortality or first cardiac hospitalization, all-cause mortality or first infectious hospitalization, all-cause mortality or first decline in serum albumin, and nonvascular access-related hospitalizations in the entire cohort. There was, however, a 20% reduction in cardiac deaths associated with the high-flux group.

Analysis of statistical interactions of the treatment interventions with the seven prespecified baseline characteristics (age, gender, race, diabetes, years on dialysis or vintage, comorbidity assessed by the index of coexistent disease score, and serum albumin concentration) was also performed. For the dose intervention, the only interaction that was statistically significant was that with gender ($p = 0.014$); however, this interaction was only significant without considering corrections for multiple comparisons.[24] Thus, women randomized to the high-dose group had a lower mortality rate than women randomized to the standard-dose group (relative risk or RR of all-cause mortality of 0.81; $p = 0.02$), whereas men randomized to the high-dose group had a nonsignificant increase in mortality rate compared with men randomized to the standard-dose group (RR of 1.16; $p = 0.16$). Although the mean body size was different between men and women, the different effects of high-dose dialysis on mortality between women and men persisted after adjustment for the modeled urea distribution volume or other body size parameters such as body weight and body mass index. Thus, this analysis suggested that women respond to high-dose dialysis differently than men, not because of differences in body size, but because of some yet unidentified factors. This difference was accentuated in white patients, but was essentially absent in black patients.[24]

Besides gender, there were no significant interactions between other baseline factors and the dose intervention for all-cause mortality. It is important to emphasize that there were no interactions of dialysis dose with age, diabetes, other comorbidities, or serum albumin concentration, suggesting that increasing the dialysis dose does not prolong survival in patients who are older, who have diabetes, or who have other comorbidities, similar to the lack of effect observed in patients without these conditions. This notion was novel and was contrary to certain previous observational studies (see for example those reviewed in previous K/DOQI guidelines).[25]

Statistical interactions of the flux intervention and dialysis vintage were statistically significant ($p = 0.005$), even after correction for multiple statistical comparisons.[26] Thus, patients who had been previously dialyzed for more than 3.7 years before entry into the HEMO Study and were randomized to the high-flux group had a 32% lower all-cause mortality rate than similar patients randomized to the low-flux group (RR of 0.68, $p = 0.001$). In contrast, patients who had been previously dialyzed for less than 3.7 years and were randomized to the high-flux group had a mortality rate similar to those randomized to the low-flux group (RR of 1.05, $p = 0.55$). This interaction did not appear to be driven by differences in residual kidney clearance between the high-vintage and low-vintage groups. Finally, it should be noted that this effect of high-flux hemodialysis on all-cause mortality was considerably weakened when the years on dialysis during the follow-up phase of the study were combined with the prestudy years on dialysis. Besides dialysis vintage, there were no significant interactions between other baseline factors and the flux intervention for all-cause mortality.

In summary, the results from the HEMO Study showed that increasing the dose of dialysis (above a single-pool value of 1.32 or an equilibrated value of 1.16) or using a high-flux membrane dialyzer does not decrease all-cause mortality in the entire cohort. Nevertheless, certain patient subgroups may benefit from increasing the dialysis dose or using a high-flux membrane. These latter conclusions must be tempered by the realization that the data were derived from only secondary analyses of the trial.

Membrane Permeability Outcome Study

According to the entry criteria, patients participating in the HEMO Study were required to have limited residual kidney function (urea clearance $\leq$1.5 ml/min/1.73 m^2 or less) and were therefore largely prevalent patients. This restriction was intentional because of the concern that significant residual kidney clearance might mask the effect of the various randomized dialysis interventions. In contrast, the MPO Study hypothesized that the effect of membrane permeability or flux on patient outcome might be different in incident than in prevalent patients, perhaps because of early survival bias. The main findings from this study have only recently been published.[27]

The MPO Study was a prospective, multicenter clinical trial that randomized 738 incident chronic hemodialysis patients to be treated by either a low-flux membrane dialyzer (ultrafiltration coefficient <10 ml/mmHg per hour and sieving coefficient for β_2-microglobulin equal to 0) or a high-flux membrane dialyzer (ultrafiltration coefficient >20 ml/mmHg per hour and sieving coefficient for β_2-microglobulin >0.6). Both synthetic and cellulosic (modified and unmodified) membranes were permitted in the study, in contrast to the HEMO Study in which unmodified cellulosic membranes were excluded. The patients were dialyzed to achieve a urea spKt/V of >1.2 in both randomized groups. Dialyzer reuse was not allowed, and treatment time was a minimum of 3 hours. The primary outcome of this study was all-cause patient mortality.

The study was complicated by a change in the protocol approximately 1 year after the study had been initiated. Originally, the study was designed to examine only patients with a baseline serum albumin $\leq$4 g/dl or less. Because of difficulties in patient recruitment, however, the enrollment was extended to include patients with any levels of serum albumin levels, but with the analysis stratified according to serum albumin levels $\leq$4 g/dl or less and >4 g/dl, respectively. After patient recruitment for 4.5 years, the study was completed with at least 3 years of follow-up obtained on each patient. More details of the study design and protocol have been published elsewhere.[28,29]

The patients were recruited from 59 dialysis centers in nine European countries. Of the 738 patients initially recruited into the study, 647 were eligible to be included in the analysis. The patients were representative of 21st century dialysis populations in developed countries; however, there were only 26.9% diabetic patients in the study population, which was lower than the percentage in the US ESRD population and those included in the HEMO Study. The

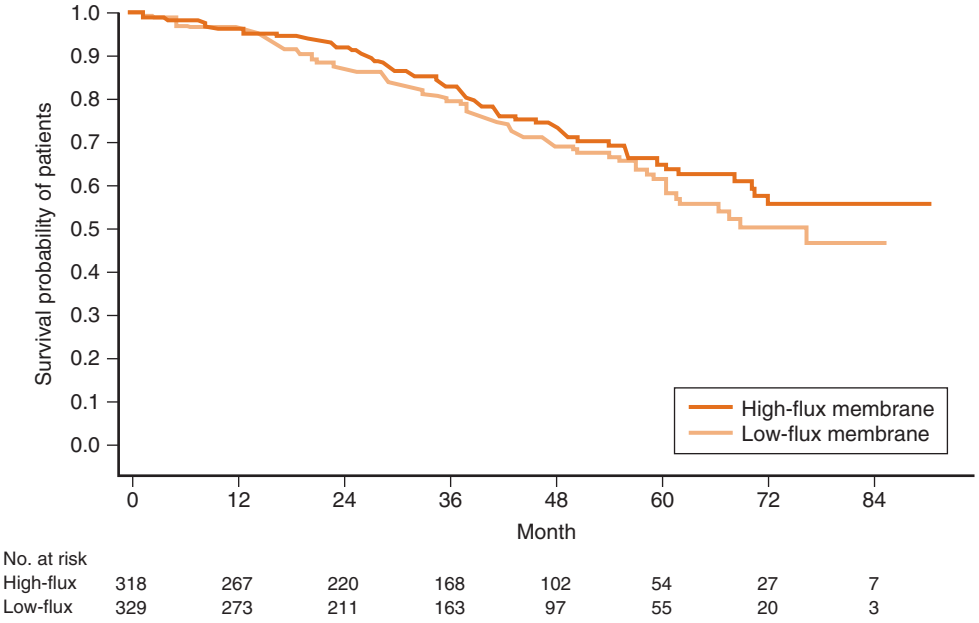


FIGURE 22-2 Kaplan-Meier survival curves for the randomized intervention in the Membrane Permeability Outcomes (MPO) Study. The curves are unadjusted for other covariates. All-cause mortality in the high-flux group was not different ($p = 0.214$) from that in the low-flux group. (Reproduced with permission from F. Locatelli, A. Martin-Malo, T. Hannedouche, et al., Effect of membrane permeability on survival of hemodialysis patients, J. Am. Soc. Nephrol. [2008].)

mean observation period was 3 years and the maximum was 7.5 years. The crude morality rate was 8.2 deaths per 100 patient-years. Kaplan Meier survival curves for the low-flux and high-flux groups are shown in Figure 22-2. When all patients were evaluated together, independent of the serum albumin concentration at enrollment, there was no significant difference in mortality for patients treated by either a low-flux or high-flux membrane. After correction for patient age, gender, presence of diabetes, other comorbidities, and type of vascular access, there was a trend for a lower risk of death in patients treated by the high-flux membrane by 24%, but this difference was not statistically significant ($p = 0.091$). There were no differences in the rate of hospital admissions among patients treated with either low-flux or high-flux membrane dialyzers. As expected, serum β_2-microglobulin levels increased from month 0 to month 36 to a lesser extent ($p < 0.05$) in the high-flux group (4.4 ± 7.8 mg/L) than in the low-flux group (8.0 ± 12.3 mg/L).

Because of the original study design, the analysis was also stratified according to the baseline serum albumin levels. In the group with initial serum albumin levels $\leq$4 g/dl or less (N = 493), the use of high-flux membrane dialyzers in fact resulted in a 37% reduction in mortality ($p = 0.01$). In the patients with baseline serum albumin of >4 g/dl (N = 154), however, there was no significant difference in the mortality of between the low-flux and high-flux groups. Despite the original study design of restriction in serum albumin inclusion, these are secondary analyses and must be cautiously interpreted. In an additional posthoc secondary analysis, diabetic patients treated using a high-flux membrane dialyzer (N = 83) had a 38% reduction in the RR of death ($p = 0.056$), compared to diabetic patients treated using a low-flux membrane dialyzer (N = 74). These secondary analyses suggest different conclusions than those from the HEMO Study where there were no differences in the effects of membrane flux between patients stratified by serum albumin concentrations or between patients stratified by diabetic status. It is unclear whether these apparently different observations between the HEMO Study and the MPO Study were due to the differences between incident and prevalent patients or in other aspects of hemodialysis treatments in European and U.S. dialysis centers; nonetheless, these findings are provocative and collectively suggest a beneficial effect of high-flux hemodialysis.

The intent of the MPO Study was to enroll a fragile patient population, as reflected by low serum albumin concentrations, to increase the likelihood that high-flux dialysis would improve clinical outcomes. The crude mortality rate of 8.2 deaths per 100 patient-years observed in this study was, however, substantially lower than expected (14–26 per 100 patient-years in Europe and 24 per 100 patient-years in the United States), likely because the patients were incident and had substantial residual kidney function (71.9% of patients had urine volumes >100 ml/day). This suggests that the intent to enroll more fragile patients in this study might not have been entirely met. Second, it has been suggested that clearances of β_2-microglobulin for the high-flux membrane dialyzers used in the MPO Study might have been substantially higher than those used in the HEMO Study, because dialyzer reuse was not allowed in the former. This hypothesis could not be definitively confirmed because β_2-microglobulin clearances were not measured in the MPO Study. Interestingly, differences in the increase in serum β_2-microglobulin levels during the first 3 years of treatment between the low-flux and high-flux groups in the MPO Study of 3.6 mg/L (8–4.4 mg/L, assuming that the mean baseline serum β_2-microglobulin levels were identical in both study groups) was less than the separation in serum β_2-microglobulin levels in the HEMO Study of 8 mg/L (41.5–33.5 mg/L).[30] Such differences are at least partially expected because many patients in the MPO Study had substantial residual kidney function at the beginning of the study that reduced any differences in serum β_2-microglobulin levels. Nonetheless, further critical comparisons of the data from the HEMO and MPO trials of dialysis membrane flux may prove more informative.

DIALYSIS DOSE AS ASSESSED BY UREA CLEARANCE

The dose of small solute clearance, urea Kt/V, described previously, in relation to clinical outcome of hemodialysis patients requires further discussion. Because it is the primary prescription parameter in current guidelines for hemodialysis adequacy,[31–33] it is commonly referred to simply as the dialysis dose and will be described as such in this section. Although the relationship between urea Kt/V and serum urea concentrations during hemodialysis treatment and the interdialytic interval are well-established,[34,35] the relationship between urea Kt/V and urea removal is not always apparent. It should be emphasized that urea Kt/V does not measure the absolute amount of urea removed; rather, it is a measure of the *"relative"* amount of urea removed during the hemodialysis treatment. This can be observed in the following approximate equality:

$$(1) \qquad Kt/V = Kt/V \times (TAC_{urea}/TAC_{urea}) \approx (Kt \times TAC_{urea})/(V \times TAC_{urea})$$

This equation states that urea Kt/V is a ratio of the amount of urea removed during the treatment ($Kt \times TAC_{urea}$) relative to the *"average"* amount of urea mass in the body ($V \times TAC_{urea}$). Thus, urea Kt/V is a relative measure of urea removal, even though it is not obvious by its mathematical expression. It has been suggested that urea Kt/V is a ratio of the amount of urea removed divided by the total amount of urea in the body at the beginning of treatment and therefore cannot be greater than unity.[36] The suggestion that urea Kt/V is an illogical or flawed construct is simply untrue. The previous equation would be exact if TAC_{urea} was identical during both the intradialytic and interdialytic intervals and the urea distribution volume was constant.

The popularity of urea Kt/V as a dialysis dose parameter began with the mechanistic analysis of the NCDS,[19] and a main reason for its common use is that several observational studies in the 1990s showed associations of poor hemodialysis patient survival with low values of urea Kt/V.[37–39] It is proposed by several national and international guidelines and mandated by regulatory agencies that routine measurements of dialysis dose should be performed at least monthly.[31–33]

Measurement of Dialysis Dose

The current recommended procedure for determining dialysis dose is the measurement of predialysis and postdialysis serum urea or BUN concentrations during the same treatment session. Detailed descriptions of these recommended procedures have been documented in the previous Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines[25,32] and will be summarized here only.

The predialysis blood sample must be taken before the hemodialysis session has started and care must be taken not to dilute this sample with either heparin or saline solutions in the dialysis tubing. A brief description of postdialysis rebound of BUN is necessary to understand the importance of timing for collecting the postdialysis blood sample. The kinetics of postdialysis rebound of BUN is illustrated in Figure 22-3.[40] There are three distinct mechanisms that contribute to a rapid increase in BUN after stopping the treatment when using an arteriovenous (AV) fistula or graft. Immediately after stopping the hemodialysis treatment, blood sampled from the blood access may contain substantial amounts of recirculated blood from two different components: 1) access recirculation and 2) cardiopulmonary recirculation.[41] Access recirculation occurs when the blood flow rate to the dialyzer exceeds the flow rate within the access, and cardiopulmonary recirculation is always present to various degrees when using an AV fistula or graft.[42] Both of these components disappear during the first few minutes after stopping the treatment. To clear the dead space between the access and the blood sampling port in the extracorporeal circuit, it is convenient not to stop the blood flow to the dialyzer completely, but rather to lower the blood flow rate substantially, commonly to around 100 ml/min. After slowing the blood flow rate, the postdialysis rebound as a result of access recirculation will resolve in approximately 15–20 seconds, and the cardiopulmonary component will

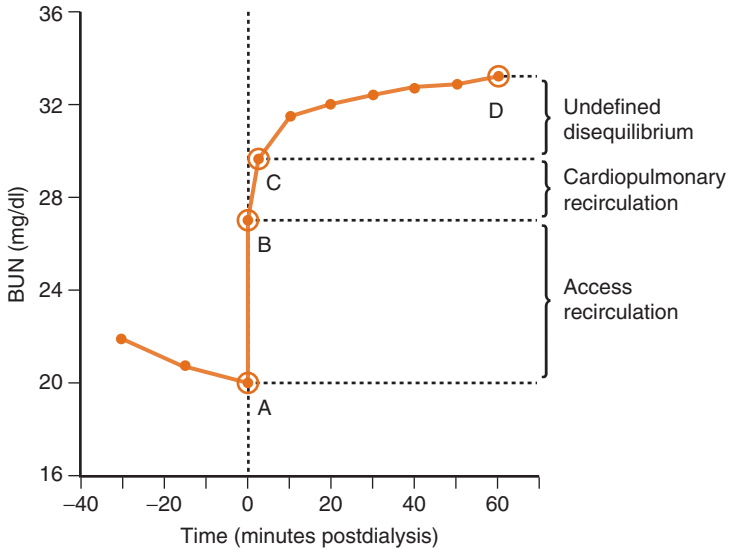


FIGURE 22-3 Schematic diagram of the increase in systemic blood urea nitrogen (BUN) concentration immediately after stopping hemodialysis. These changes are not due to urea generation within the body but largely due to the redistribution of urea within its distribution volume. The undefined disequilibrium described in the figure is also known as remote compartment rebound. The labels *A, B, C,* and *D* indicate potential samples times. (Reproduced with permission from T.A. Depner, Assessing adequacy of hemodialysis: urea modeling, Kidney Int. 45 [1994] 1522-1535.)

resolve in 2–3 minutes. The last mechanism of postdialysis rebound of BUN is due to the disequilibrium of urea among different cellular or perfused body compartments. This mechanism remains incompletely understood and has recently been termed remote compartment rebound.[32] Regardless of the mechanism(s), this disequilibrium, hence the BUN rebound, takes considerably longer (30 to 60 minutes) to resolve.

One recommended procedure for obtaining the postdialysis blood sample is to wait at least 15 seconds after slowing the blood pump speed to eliminate the effect of access recirculation.[32] On the other hand, if there is a longer waiting period beyond 15–20 seconds, more postdialysis rebound will occur, a higher BUN concentration will be measured, and a lower estimate of urea Kt/V will be calculated. If an equilibrated estimate of urea Kt/V is desired, the blood sample should be taken 15–20 seconds postdialysis because rate equations used to calculate eKt/V correct for both cardiopulmonary and remote compartment rebound (see later text).

In clinical practice, various methods have been used to calculate an estimate of the dialysis dose, and these various dialysis dose parameters are similarly associated with patient outcome. The differences among these methods depend on the ease and accuracy of computation. The methods also differ in the amount of data to be collected and the assumptions made in the calculations.

A rigorous method for calculating urea Kt/V from predialysis and postdialysis BUN concentrations is formal urea kinetic modeling, a method first devised by Gotch and Sargent.[35] The original version of formal urea kinetic modeling required a third BUN sample, obtained predialysis at the subsequent dialysis session. Since that time, however, an alternative method that does not require a third blood sample was devised,[43] but this calculation method is practically complex. Nonetheless, formal urea kinetic modeling is considered advantageous because it allows for advanced troubleshooting of inadequate doses of dialysis. A relatively simple alternative is to use an approach developed by Daugirdas[44] that permits calculation of urea Kt/V from the postdialysis to predialysis BUN concentration ratio (R), the treatment time t (in hours), and the intradialytic decrease (Δ) in body weight (BW) as defined in the following equation:

$$(2) \qquad Kt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times \Delta BW/BW$$

where ln denotes the natural logarithm function. This equation approximately accounts for the reduction in urea distribution volume and urea generation during the treatment. It is highly accurate for clinical purposes from treatments between 2.5 and 5 hours in length,[44] compared to formal kinetic modeling. Care should be applied in situations in which treatment times lie outside this range. Further, it is not easy to calculate the protein catabolic rate when using this approach. Nonetheless, the equation shown previously is very practical and provides excellent estimates of urea Kt/V during routine thrice-weekly hemodialysis.

More often, dialysis units submit blood samples for analysis to an independent laboratory that computes an estimate of urea Kt/V using only the predialysis and postdialysis BUN concentrations as inputs without additional treatment data, such as treatment time or predialysis and postdialysis body weight. Such estimates are therefore only modified values of the urea reduction ratio (URR, defined as one minus the postdialysis to predialysis BUN concentration ratio, often expressed as a percentage), and the calculated urea Kt/V values are only estimates based on empirical correlations. Clinicians should be aware of the methods for obtaining postdialysis blood samples and the methods to calculate urea Kt/V for their patients. Recent data from the Quality European Studies initiative suggest that attention to these methods are necessary.[45]

Finally, an additional method for evaluating the dialysis dose that is gaining popularity should be mentioned. This approach measures dialyzer instantaneous clearances at any time during a given treatment and is known as on-line clearance. The advantage of this approach is that a clearance determination can be made at each treatment without additional cost, because no blood sampling or assay is necessary. This method is based on the assumption that transmembrane movement of small electrolytes, mostly sodium, correlate with transmembrane movement for urea, such that clearances measured by changes in dialysate conductivity correlate with clearances for urea.[46] There are at least two commercial devices that can be used for such purposes; the results from both these devices are comparable and useful clinically.[47] The major disadvantage with such devices is the difficulty in accurately estimating the urea distribution volume so as to calculate Kt/V from the measured dialyzer clearance or K. Although anthropometric equations can be used to estimate urea distribution volume (which approximates total body water volume), several studies have shown that these anthropometric values overestimate the volumes of distribution estimated by urea kinetic modeling.[48,49] While notable progress continues to be made with this approach,[50–52] the consistency between Kt/V measured from urea kinetic modeling and that measured from on-line clearances remains incompletely understood.

Equilibrated Kt/V Versus Single-Pool Kt/V

The dialysis dose parameter calculated from predialysis and postdialysis BUN as described previously is called the single pool Kt/V (spKt/V) because it is calculated assuming that urea is equally distributed in a single compartment, often assumed to be approximately equal to total body water volume. As illustrated in Figure 22-3, however, the postdialysis BUN continues to rebound for 30–60 minutes after stopping the treatment. The BUN concentration in a blood sample obtained at 30 to 60 minutes postdialysis yields a calculated parameter known as the equilibrated Kt/V (eKt/V). There are two compelling reasons for using eKt/V instead of spKt/V. First, eKt/V is a more accurate estimate of a given dose of urea removal from the patient.[53] Thus, identical spKt/V values obtained in the same patient may be associated with different eKt/V values, if there are differences in the duration of dialysis sessions resulting in differences in the magnitude of postdialysis rebound in BUN concentrations. Second, the dose intervention in the HEMO Study, the largest randomized trial of dialysis dose, was guided using eKt/V, not spKt/V, values. It can be argued that the results from the HEMO study do not rigorously apply when using spKt/V to dose therapy.

Waiting 30 to 60 minutes after stopping the treatment for measuring the equilibrated urea concentration is not

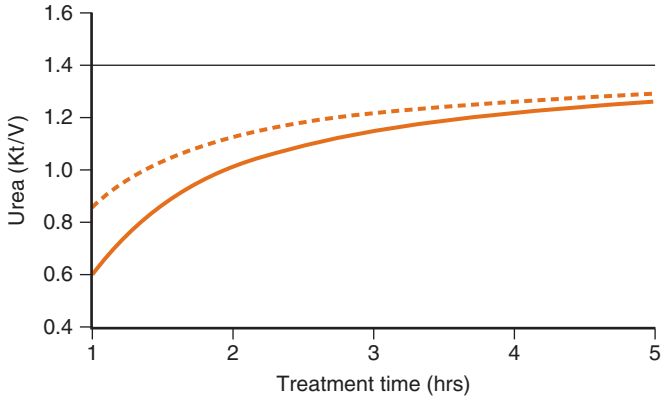


FIGURE 22-4 The relationship between urea equilibrated Kt/V (eKt/V) and treatment time at a constant urea spKt/V of 1.4 (*solid line*). The corresponding eKt/V values are corrected for postdialysis rebound using either the Daugirdas-Schneditz rate equation[54] or the HEMO Study rate equation[55] and shown as the dashed and dotted lines, respectively. As treatment time increases, there is less postdialysis rebound in systemic BUN concentration; hence the eKt/V approaches the fixed spKt/V value. (Reproduced with permission from J.K. Leypoldt, A.K. Cheung, Revisiting the hemodialysis dose, Sem. Dialysis 19 [2006] 96-101.)

practical. The reported findings of the HEMO Study are that the effect of dose on patient outcomes, if present, is unlikely to be large, at least within the ranges of spKt/V between 1.32 and 1.71 or eKt/V between 1.16 and 1.53. Thus, precise dose targeting does not appear to be necessary in the majority of hemodialysis patients. According to this thesis, routine monitoring of hemodialysis patients using spKt/V to guide therapy should be sufficient. Figure 22-4 illustrates how spKt/V can be used to guide routine therapy yet achieve an adequate eKt/V. If a minimum value of urea spKt/V of 1.4 is delivered to all patients, the eKt/V values would depend on treatment time and on the equation used to correct for postdialysis rebound of BUN concentration. The concept of using the rate of BUN removal (i.e., clearance) or intensity of dialysis therapy to calculate eKt/V from spKt/V was first proposed by Daugirdas and Schneditz[54] in 1995. They proposed that eKt/V could be calculated from spKt/V values and treatment times using the following rate equation:

$$(3) \qquad eKt/V = spKt/V - 0.6 \times (spKt/V)/t + 0.03$$

This equation was validated in several small studies to accurately estimate eKt/V and was in fact used in the HEMO Study for precise dose targeting (note that this equation and this discussion apply to an AV access only, not a venous access; detailed considerations for a venous access are described elsewhere[25,32]). Retrospective analysis of the larger database available in the HEMO Study using eKt/V calculated from the BUN concentrations in equilibrated (30-minute) postdialysis samples as a gold standard showed, however, that eKt/V values were more accurately estimated using the alternative rate equation.[55]

$$(4) \qquad eKt/V = spKt/V - 0.39 \times (spKt/V)/t$$

The correction factor used to estimate eKt/V from spKt/V is smaller in the latter equation than in the Daugirdas and Schnediz rate equation. Figure 22-4 plots eKt/V values predicted using these rate equations for a fixed value of spKt/V of 1.4. Using the HEMO Study rate equation, eKt/V would be greater than 1.16 (the achieved mean of the standard-dose arm) as long as the treatment time is longer than 2 hours and 18 minutes. If a higher dose target is deemed desirable, eKt/V values of greater than 1.53 (the achieved mean of the high-dose arm) would be attained for a spKt/V of 1.8 as long as the treatment time is longer than 2 hours and 36 minutes.[56] Since the minimum treatment time allowed in the HEMO Study was 2 hours and 30 minutes, the findings from the HEMO Study may be applicable to such treatment times.

Based on the previous discussion of the advantages and disadvantages of using spKt/V and eKt/V to monitor routine therapy, it is not surprising that expert groups differ in their recommendations. For example, the 2006 K/DOQI Guidelines recommend monitoring spKt/V,[32] whereas the 2007 European Best Practice Guidelines recommend monitoring eKt/V.[33] Each clinician should make an individual choice that is practical for the local circumstances, because there does not appear to be substantial advantage of one parameter over the other for the prediction of clinical outcomes.

Preferred Dialysis Dose Guidelines

More recent, large observational studies of the association between dialysis dose and hemodialysis patient survival have extended studies from the 1990s. These studies in general suggest that higher doses of dialysis, equivalent to those in the high-dose arm of the HEMO Study, are associated with lower mortality.[57,58] The results from these observational studies are somewhat different from the primary results in the HEMO Study, which showed no significant difference in mortality between the group randomized to the standard dose (target eKt/V of 1.05 and achieved eKt/V of 1.16) and the group randomized to the high dose (target eKt/V of 1.45 and achieved eKt/V of 1.53). Additional secondary analyses from the HEMO Study also failed to show a benefit of higher dialysis doses on nutritional indices, such as body weight and serum albumin concentration,[59] or quality of life measures.[60] A possible resolution of these seemingly conflicting findings between the observational studies and the HEMO Study is provided in the as-treated analyses on dialysis dose from the HEMO Study.[61] This latter study demonstrated a strong relationship between achieved dialysis dose and outcome within both the standard-dose and the high-dose arms, as observed in previous observational studies; however, the high magnitude of this increased death risk for lower dose within each arm (37%–58% higher death risk for each 0.1 lower value of eKt/V) appeared to be incompatible with a biological effect. This apparent association of dialysis dose on survival was identified as a dose-targeting bias of such observational studies.[61] This latter analysis has therefore questioned the validity of previous observational studies regarding the influence of dialysis dose on hemodialysis patient mortality.

Several expert groups have produced clinical practice guidelines based on these studies. For example, the K/DOQI Clinical Practice Guidelines recommend that dialysis dose be monitored using spKt/V, and they suggest the minimum dose be 1.2 with a target dose of 1.4.[32] A target dose of 1.4 is designed to ensure that a large fraction (97%) of patients will achieve the minimum dose of 1.2. In contrast,

the European Best Practice Guidelines recommend that dialysis dose be monitored using eKt/V, and they recommend a target dose of 1.2.[33] Since a target eKt/V of 1.2 is approximately equivalent to a target spKt/V of 1.4, it can be appreciated that these recommendations are very similar to each other.

Body Size

Work by several researchers has challenged whether dialysis dose as assessed by urea Kt should be normalized to V when prescribing hemodialysis therapy. Chertow and colleagues[62] showed that the RR of mortality among hemodialysis patients did not decrease monotonically with increasing Kt/V or URR. Specifically, patients with a URR lower than and those with a URR higher than the middle quintile of URR (64.1%–67.4%) had an elevated RR of death. This J-shaped relationship does not support the concept that URR or Kt/V is an ideal outcome-based measure of dialysis dose. These investigators also noted that the RR of death decreased monotonically with increasing dialysis dose when expressed as Kt and not normalized to body size. Subsequently, Lowrie and colleagues[63] showed that the odds of patient death decreased with increasing Kt and with increasing body size, suggesting that Kt and V are separate parameters for evaluating patient outcomes. More recently, such relationships have been further explored using different measures of patient size in a very large database.[64] These studies point out that small patients may be susceptible to underdialysis when Kt/V is used for prescribing hemodialysis treatments because their V is small.

Confirmation that body size is an important determinant of patient mortality comes from additional data analyses from the U.S. Renal Data System (USRDS) by Wolfe and colleagues[58] and Port and colleagues.[57] While confirming an inverse relationship between Kt/V and mortality, these authors also showed that, for any given Kt/V, a smaller body size is associated with higher mortality. Thus, the analyses by Lowrie and colleagues[63,64] and others[57,58] collectively establish that patient mortality depends on both body size and a dialysis dose parameter; however, these investigators differ on whether the dialysis dose should be assessed by either Kt or Kt/V.

It is unlikely that the optimal choice of dialysis dose measures can be determined by further outcome studies and will likely be determined by practical considerations. Urea Kt/V and the URR were readily adopted by the dialysis community because they could be easily calculated from the predialysis and postdialysis BUN concentrations without the need to separately evaluate V; for example, see the equation (2). Until recently, calculation of Kt required first calculating Kt/V and then multiplying this parameter by an independent estimate of V. The recent availability of automated determinations of Kt by calculating the conductivity (or on-line) clearance multiplied by treatment time permits a simple determination of Kt during each treatment. At the present time, either Kt/V or Kt appears to be a reasonable measure of dialysis dose for monitoring the adequacy of dialysis therapy. When monitoring dialysis dose by Kt/V, however, care should be taken not to underdialyze small patients. In contrast, when measuring dialysis dose using Kt, care should be taken not to underdialyze large patients.

Gender

The results reported by the HEMO Study suggest that the relationship between all-cause mortality and dialysis dose differs between men and women (see previous). Recent observational data from the USRDS also support the notion that women treated by thrice-weekly hemodialysis benefit from a higher dose of dialysis, whereas men do not.[65] It should be noted that Lowrie and colleagues[63] also found that different dose targets were necessary for men and women when using Kt instead of Kt/V as the dialysis dose measure. Collectively, these observations indicate that gender should be considered when prescribing the dose of dialysis.

Recently, two groups of investigators[66–68] have considered the clinical implications of normalizing the dialysis dose (Kt) by parameters other than V for both men and women. Both groups have used anthropometric equations to estimate V and body surface area (BSA) for large cohorts of hemodialysis patients and then computed various normalized dose parameters, including Kt/V, Kt, $Kt/V^{0.67}$ and Kt/BSA for these patient cohorts. Assuming that $Kt/V^{0.67}$ or Kt/BSA represents the gold standard for dose, these calculations showed that women and small men would be underdialyzed if dialysis dose was prescribed using current guidelines, that is, achieving a minimum spKt/V of 1.2. These theoretical findings are consistent with the previous analyses of the effects of body size and gender and suggest using caution when prescribing the dose of dialysis to women and small men at marginally low values of Kt/V.

The conservative interpretation of these findings, which is to do no harm to the patient, would be to deliver a high dose of dialysis (spKt/V of 1.8 or eKt/V of 1.53) to women, but not necessarily to men. This interpretation has not been accepted by K/DOQI Guidelines;[32] however, the European Best Practice Guidelines do recommend higher dialysis doses in women (eKt/V of 1.4 instead of 1.2).[33]

EFFECT OF TREATMENT TIME

It is important to discuss treatment time (session duration) as an independent adequacy parameter for thrice-weekly hemodialysis therapy under two different situations. The first situation would be when treatment times are in the range of routine thrice-weekly hemodialysis (3–5 hours); the second would be for significantly longer treatment times, for example, up to 8 hours. These separate situations will be addressed sequentially below. Treatment time is a practical hemodialysis prescription parameter; however, interpretation of the effect of treatment time on patient outcomes can be difficult because this parameter can influence both the ability to remove fluid during therapy and the clearance of middle molecules.

The only large randomized trial to examine treatment time during hemodialysis (3–5 hours/session) was the NCDS. As previously mentioned, the effect of treatment time on patient outcomes in that study was not considered to be statistically significant.[11] It is difficult to translate a treatment time effect in the NCDS to current hemodialysis practices because of the substantial differences in practice patterns between the 1970s and the 21st century. The results

from several observational studies regarding the association between treatment time and patient outcomes have arrived at different conclusions. Some of those studies, however, suffered from methodological concerns such as not controlling for the effect of dialysis dose[69] or evaluating only a very limited range of hemodialysis treatment times.[70]

Three recent observational studies used more rigorous methodologies and reached similar conclusions. Saran and colleagues[71] reported the association of longer treatment time and dialysis dose (urea spKt/V) with clinical outcomes on 22,000 hemodialysis patients from seven countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). They showed that both higher urea Kt/V and longer treatment times were independently associated with lower death risk. The results were consistent in each of the three regions: Japan, Europe, and the United States. For all countries combined the adjusted risk of all-cause mortality was 19% lower ($p = 0.0005$), but the magnitude of this effect varied among regions. For every additional 30 minutes of treatment time, the RR of all-cause mortality was 4% lower in the United States, 6% lower in Europe, and 16% lower in Japan. A significant statistical interaction was found between Kt/V and treatment time in the multivariate survival models ($p = 0.007$), indicating that a longer treatment time was even more beneficial at higher values of Kt/V. These authors suggested that longer treatment times may improve hemodialysis patient outcomes by improving control of body fluids because higher ultrafiltration rates (total ultrafiltration volume divided by treatment time) were independently associated with an elevated risk of mortality (9% for every increase in ultrafiltration rate of 10 ml/h/kg; $p = 0.02$).

Marshall and colleagues[72] also reported associations of patient mortality with both urea Kt/V and treatment time using data from the Australian and New Zealand Dialysis and Transplant Registry. In this cohort, treatment times were categorized into 5 groups: <3.5 h, 3.5–3.9 h, 4–4.4 h, 4.5–4.9 h and >5 h. Shorter treatment times were associated with higher risk of mortality. Urea Kt/V between 1.3 and 1.39 and treatment time between 4.5 and 4.9 hours were independently associated with the lowest risk of all-cause mortality. Compared to treatment times between 4 and 4.4 hours, longer treatment times between 4.5 and 4.9 hours were associated with a 20% risk reduction ($p < 0.05$) in all-cause mortality. Since membrane flux was reported to be not associated with mortality risk in that study, it was unlikely that the effect of treatment time was due to improved middle molecule clearances; rather, improved control of body fluid volume was likely to be the best explanation for this association between treatment time and patient survival.

Finally, Kalantar-Zadeh and colleagues[73] have examined the effect of fluid retention on 2-year patient survival in 34,107 hemodialysis patients in the United States. In unadjusted analyses, higher interdialytic weight gains were associated with better nutritional status and better survival. When the associations were adjusted for malnutrition-inflammation surrogates, however, higher weight gains were associated with increased risk of higher all-cause and cardiovascular mortality. The risks of cardiovascular mortality were substantially lower (RR = 0.67) for weight gains <1 kg and substantially higher (RR = 1.25) for weight gains ≥4 kg or greater, compared to the reference group with weight gains between 1.5 and 2 kg.

These studies collectively suggest that adequate fluid removal is important and that the longer treatment time improves survival at least partially through this mechanism. Since these studies were observational in nature, however, the causality of increased treatment time on clinical outcome could not be inferred. Nonetheless, it seems reasonable to lengthen hemodialysis treatment time up to 5 hours per session for patients with cardiovascular or hemodynamic instability[74] or in the elderly.[75] It is also important to note that increasing treatment time during thrice weekly hemodialysis is one approach for enhancing phosphate removal.[76]

The experience from individual centers in extending treatment times substantially greater than conventional times, such as 8 hours, deserve mention. These long treatment times cannot be readily accommodated easily in all dialysis centers, although attempts are being made to dialyze patients overnight with such schedules.[77–79] The excellent outcomes that were achieved with very long (8 hour) treatment times, such as those from Tassin, France, are encouraging, although these were not results from randomized clinical trials.[80] These patients received very high dialysis doses and achieved lower body fluid volumes and blood pressure, because of the slow removal of fluids during the long dialysis sessions.[81–85] Because those patients were treated primarily with low-flux membrane dialyzers, however, it is unlikely that those excellent clinical results were due to improved middle molecule removal (high-flux dialysis for 3.5 hours thrice weekly would remove substantially more β_2-microglobulin than low-flux dialysis for 8 hours thrice weekly). Patient selection, such as those who were motivated and compliant, could potentially be a contributory factor. It remains to be seen if long nocturnal thrice-weekly hemodialysis is practical and will be accepted by a large proportion of the hemodialysis population.[77–79]

MIDDLE MOLECULE CLEARANCE DURING HEMODIALYSIS

Quantification of Middle Molecule Clearance

Although treatment time has been used as a surrogate measure for the removal of middle molecules during hemodialysis, this concept is based on the premise that the dialysis membranes considered had identical surface area and permeability to middle molecules. To account for dialysis membrane properties, it is more appropriate to directly evaluate the clearance of a marker solute in the middle molecular range. The middle molecule that has historically been used as a marker molecule is vitamin B_{12}, and calculated in vitro dialyzer clearance of vitamin B_{12} has been shown to be an independent predictor of survival among chronic hemodialysis patients in one observational study.[86] Dialyzer clearances of this solute, however, can only be accurately evaluated in vitro because of its extensive binding to plasma proteins. The causative role of β_2-microglobulin in the pathogenesis of dialysis-related amyloidosis,[87] and its ready measurement in the serum or plasma of ESRD patients have resulted in the use of β_2-microglobulin as a marker solute for evaluating the clearance of middle molecules in more recent studies.

Kinetic modeling of β_2-microglobulin during hemodialysis follows the same general principles as those for urea. When modeling β_2-microglobulin, however, different simplifying assumptions are required. The following assumptions are a reasonable starting point:

1. β2-microglobulin is uniformly distributed in a single compartment that approximates extracellular fluid volume.[59] This assumption neglects postdialysis rebound of plasma β2-microglobulin concentration.
2. Fluid removed during hemodialysis treatment originates entirely from the extracellular fluid volume.
3. The amount of β2-microglobulin generated intradialytically can be neglected.
4. There is no residual renal or extrarenal clearance of β2-microglobulin.

Based on these assumptions, a mass balance equation for β_2-microglobulin within the patient can be integrated over the intradialytic period.[88] From that solution, the following equation was derived to calculate the mean dialyzer clearance of β_2-microglobulin ($K_{\beta 2m}$) during the hemodialysis session using predialysis and postdialysis concentrations, C(0) and C(T), respectively:

$$(5)\quad K_{\beta 2m} = Q_f(1 - \ln [C(T)/C(0)/\ln [1 + Q_f \times T/V(T)]$$

where Q_f is the ultrafiltration rate determined as the difference between the predialysis and postdialysis body weights divided by treatment time and V(T) is an estimate of extracellular fluid volume (often estimated as either one third of urea distribution volume or 20% of body weight) at the end of the hemodialysis session. This equation was used to evaluate dialyzer clearances of β_2-microglobulin in the HEMO Study for the purpose of defining the flux intervention and examining the effect of reuse on dialyzer clearance of β_2-microglobulin.[21,26] Although valuable for certain purposes, the estimates of dialyzer clearance provided by this equation are only approximate because this model neglects postdialysis rebound of the plasma concentration of β_2-microglobulin, in addition to the other limitations discussed previously.

The postdialysis rebound of β_2-microglobulin has been examined theoretically in several publications.[89–92] It has been demonstrated that substantial postdialysis rebound of β_2-microglobulin can occur following routine hemodialysis treatment with high-flux dialyzers;[93,94] however, the magnitude and significance of the rebound in concentration remains incompletely defined. Recently, Ward and colleagues[95] developed a two-compartment, variable volume mathematical model of β_2-microglobulin kinetics and compared the predictions from this model with data obtained during and between hemodiafiltration sessions using high-flux membranes. They demonstrated that in vivo β_2-microglobulin clearances measured directly across the hemodiafilter were similar in magnitude to the intercompartmental transfer of β_2-microglobulin, suggesting that postdialysis rebound resulted from the slow transfer of β_2-microglobulin from interstitial tissues to plasma. It was concluded from this study that intercompartmental transfer of β_2-microglobulin is a significant limitation to β_2-microglobulin removal by hemodiafiltration. Additional work will be necessary to further understand the multicompartmental kinetics of β_2-microglobulin and to make them simple enough to be used clinically.

Dose of Middle Molecule Clearance

The importance of middle molecule clearance or removal on hemodialysis patient outcomes has been long debated. Several retrospective, observational studies have suggested an association between the use of high-flux hemodialysis membranes and lower patient mortality. Some reported large reductions in mortality rates associated with the use of high-flux membranes of between 19% and 76%.[96–99] In an observational study from a large registry involving 6444 patients in Italy, Locatelli and colleagues[100] reported a 10% decrease in mortality for patients treated by hemofiltration or hemodiafiltration, compared to that in hemodialysis patients treated using low-flux cellulosic membranes. The clearances of β_2-microglobulin, however, were not measured or estimated in that study. Further, the decrease in mortality was not statistically significant.

Two recent observational studies have reported reductions in mortality for patients treated by high-flux membranes. Chauveau and colleagues[101] examined the relationships between nutritional factors, membrane flux and patient survival in 650 patients from 11 different hemodialysis centers in France who were followed for 2 years. In multivariate analyses, the use of a high-flux membrane (defined as one with an in vitro ultrafiltration coefficient >20 ml/min) was associated with a statistically significant reduction of 38% in mortality. Krane and colleagues[102] performed a posthoc analysis of type 2 diabetic patients who participated in the German Diabetes and Dialysis Study, which was designed to examine the effect of statin prescription on clinical outcomes. A subgroup of 648 out of 1255 patients from that study who used the same dialysis membrane throughout the study was analyzed. Dialyzer membranes were characterized as low-flux cellulosic, low-flux semisynthetic (substituted cellulosic), low-flux synthetic, or high-flux synthetic. Low-flux dialyzers were defined as those with ultrafiltration coefficients <10 ml/h/mmHg and β_2-microglobulin clearances <10 ml/min and high-flux dialyzers as those with ultrafiltration coefficients >20 ml/h/mmHg and β_2-microglobulin clearances >20 ml/min. These investigators reported that patients treated by low-flux synthetic, low-flux semisynthetic, or low-flux cellulosic membranes had an increased RR of all-cause death of 1.59 (95% confidence interval or CI of 1.22–2.07), 2.24 (95% CI of 1.66–3.02), and 4.14 (95% CI of 2.79–6.15) respectively, compared to that for patients treated with high-flux synthetic membranes. Comparable differences were reported between these dialyzer types in the composite endpoint of death from cardiac causes, nonfatal myocardial infarction, and stroke. These findings suggest that dialysis membrane flux and/or biocompatibility are determinants of type 2 diabetic patient outcomes; these hypotheses are compatible with the posthoc secondary analyses from the MPO Study, which showed that randomization to high-flux dialysis was associated with improved survival in diabetic patients.[27]

Although the aforementioned observational studies and the MPO Study assessed the association of dialyzer type on patient outcome, neither dialyzer clearance of β_2-microglobulin nor serum β_2-microglobulin levels were routinely measured in those studies. In contrast, the HEMO Study determined these parameters regularly during the study, allowing an examination of dialyzer clearance of β_2-microglobulin and β_2-microglobulin

Kt/V of dialysis sessions and serum β_2-microglobulin levels on clinical outcomes.[30] Statistical adjustment for dialyzer type and reuse processing method was performed to eliminate confounding by these factors in these analyses. Determinants of serum β_2-microglobulin levels were then evaluated, and the clearance and Kt/V parameters were explored to examine their relationship to patient outcomes. In a multivariable regression model, baseline residual kidney urea clearance and dialyzer clearance of β_2-microglobulin were strong predictors of predialysis serum β_2-microglobulin levels. In addition, black race and dialysis vintage correlated positively, whereas age, diabetes, serum albumin level, and body mass index correlated negatively, with serum β_2-microglobulin levels. After adjustment for residual kidney urea clearance and dialysis vintage, mean cumulative predialysis serum β_2-microglobulin levels, but not dialyzer clearance of β_2-microglobulin or β_2-microglobulin Kt/V, were observed to be associated with all-cause mortality for the entire study cohort. This relationship is shown in Figure 22-5. Because low serum β_2-microglobulin levels were associated with improved all-cause mortality independent of dialyzer clearance of β_2-microglobulin, these findings suggest that enhanced generation of β_2-microglobulin may be driving this association. It is interesting to speculate that the association between higher serum β_2-microglobulin levels and poor patient outcomes is at least partially mediated by inflammation, because inflammation is associated with advanced age, comorbidity (diabetes), and low serum albumin levels, factors that are associated with high serum β_2-microglobulin levels. A recent additional analysis from the HEMO Study has reported that the association between high serum β_2-microglobulin levels and poor patient survival is related to infectious, but not cardiac, causes.[103] These analyses support the concept that the accumulation of uremic middle molecules predispose to infection and decreased survival in dialysis patients. These analyses also support the necessity to further investigate whether serum β_2-microglobulin levels should be used as a marker to guide routine prescription of chronic hemodialysis therapy.

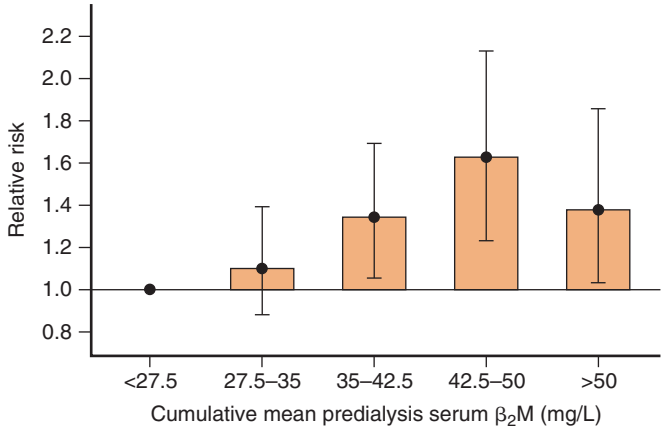


FIGURE 22-5 Association of the relative risk for all-cause mortality with predialysis serum β_2-microglobulin (β_2M) levels in the HEMO Study (N = 1813, p = 0.001). Predialysis serum β_2-microglobulin level was calculated as the mean of all of the values accumulated over time during the follow-up period. (Reproduced with permission from A.K. Cheung, M.V. Rocco, G. Yan, et al., Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the hemo study, J. Am. Soc. Nephrol. 17 [2006] 546-555.)

EFFECT OF TREATMENT FREQUENCY

Thrice weekly has remained the standard schedule for chronic hemodialysis for over 4 decades.[83] Although several pioneers have treated patients more frequently in a small number of patients, the systematic study of the frequency of hemodialysis treatments is only beginning. Currently, there are two main forms of frequent hemodialysis that are prescribed five to seven times per week. The first category is called daily or short daily hemodialysis (SDHD), defined by treatment times less than or equal to that used during conventional, thrice weekly hemodialysis. A typical SDHD prescription would be 5–6 sessions per week with each session being 3 hours or less. The second is called nocturnal hemodialysis (NHD) that is distinct from SDHD in that treatment times are typically 6–10 hours per session. Systematic reviews of clinical experiences in both NHD and SDHD were performed a few years ago; these reviews will be summarized here.

In 2005, a systematic review of the available literature regarding clinical outcomes in patients treated by NHD was performed.[104] Fourteen reports (10 papers and 4 abstracts), mostly from two groups in Toronto and London, Canada, were identified as suitable for systematic review. All of these reports were either case-control studies or prepost studies comparing changes in parameters from baseline (collected during conventional hemodialysis) to some variable time after initiation of NHD; no randomized trials were identified. A majority of these studies reported reductions in systolic, diastolic, or mean arterial blood pressure during NHD and a reduction in antihypertensive medication use. Left ventricular hypertrophy was assessed as a primary outcome in two studies.[105,106] One study showed a significant reduction in left ventricular mass; the other showed a nonsignificant reduction in left ventricular mass. Although there is general consensus that weekly phosphate clearance is increased during NHD,[107] only one of the two studies in this systematic review noted a significant reduction in serum phosphate and a reduction in use of phosphate-binding medications. The authors further stated that the interpretation of data on phosphate from clinical studies is complicated by the need to liberalize dietary protein and to add phosphate to the dialysate in some patients, to compensate for the large phosphate loss during NHD treatments. Health-related quality of life measures appeared to improve after conversion to NHD, although the degree of improvement was variable. Mixed results were observed for other outcome parameters, including measures of anemia control and calcium-phosphate metabolism.

Since the completion of this systematic review, results from three additional publications provide evidence of improved clinical outcomes in patients treated with NHD. From 2001 to 2006, five women within NHD programs in Toronto had seven pregnancies and delivered six live infants.[108] All women had previously been on thrice weekly conventional dialysis but failed to conceive. During the pregnancies, mean predialysis blood urea and mean arterial blood pressure were maintained within normal physiological parameters. The mean gestational age of the infants was 36 weeks. Although this report is limited by its sample size and the absence of a true control group, the delivery of live infants at mature gestational age is a remarkable occurrence and suggests substantial physiological improvements with frequent, long hemodialysis.

In another observational study, Pauly and colleagues[109] used data from two Canadian NHD programs and the USRDS to perform a matched analysis comparing survival between NHD and deceased and living donor kidney transplantation recipients. In this study 177 NHD patients were randomly matched to deceased and living transplant recipients in a 1:3:3 ratio and followed for a maximum of 12.4 years. During the follow-up period, the proportion of deaths among NHD patients, deceased transplant recipients, and living transplant recipients was 14.7%, 14.3%, and 8.5%, respectively. No difference in the adjusted survival between NHD patients and deceased transplant recipients was observed, whereas living transplant recipient survival was better than the other two groups. Notably, the 1-, 3-, and 5-year survival rates for the NHD patients were 96%, 90%, and 85%, respectively.

Using a randomized controlled study design, Culleton and colleagues[110] recently reported results comparing NHD to conventional thrice-weekly hemodialysis. Patients were recruited from 10 dialysis centers associated with two universities in Alberta, Canada. Only patients willing to be trained for NHD were considered eligible for enrollment. The primary outcome was the 6-month change in left ventricular mass as measured by cardiovascular magnetic resonance. Secondary outcomes were quality-of-life measures, change in systolic blood pressure, change in erythropoietin-to-hematocrit ratio, and change in calcium-phosphorus product. Twenty-seven patients were randomized to NHD and 26 were randomized to conventional hemodialysis. In the primary analysis, the left ventricular mass decreased by 13.8 $\pm$ 23 g in the NHD group but increased by 1.5 $\pm$ 24 g in the conventional hemodialysis group; this difference was statistically significant ($p = 0.04$). Although there was no indication that overall quality of life improved during NHD, there were statistically significant and clinically relevant improvements in selected kidney-specific domains in quality-of-life instruments during NHD.[111] Also, patients treated by NHD showed reductions in mean predialysis systolic blood pressure from 129 to 122 mmHg, but patients treated by conventional hemodialysis showed elevations in this same measurement from 135 to 139 mmHg. After adjustment for baseline systolic blood pressure, the mean difference between the groups increased to 14 mmHg ($p = 0.01$). This reduction in blood pressure occurred, despite a reduction in antihypertensive medications during NHD. Furthermore, there was a decrease in the serum calcium-phosphorus product during NHD, despite a reduction in oral phosphate binder use. Despite the more frequent use of the vascular access, there was no difference in vascular access-related complications, assessed by the number of bacteremic episodes, angiography, and surgical interventions between the NHD group and the conventional hemodialysis group.

Additional evidence from another randomized controlled study should become available in 2010. The Frequent Hemodialysis Network in the United States is currently conducting two NIH-sponsored studies.[112] In one study, patients are randomized to six times per week NHD performed at home or three times per week conventional hemodialysis also performed at home. Outcomes include patient survival, change in left ventricular mass using cardiovascular magnetic resonance, quality of life, and many other clinical and biochemical measures.

Numerous studies have also been reported on patients treated by SDHD; however, only 14 cohorts reported since 1998 provided clinical data that were considered relevant for systematic review.[113] Although there was one small randomized, crossover study and a few observational studies with concurrent control cohorts, most of the studies were prepost case series with analyses of changes in parameters from baseline (during conventional hemodialysis) to some variable time after initiation of SDHD without an appropriate control group. The patients previously treated by SDHD were typically young, nondiabetic, prevalent patients on conventional hemodialysis using AV fistulae or grafts as vascular access. No study evaluated mortality and only one study evaluated hospitalization rates as outcome measures. Reported findings among the studies varied considerably for most outcomes; however, two findings were relatively consistent. First, decreases in systolic blood pressure or mean arterial blood pressure were reported in 10 of 11 studies. Second, six of eight studies found no statistically significant change in serum phosphate concentration or the phosphate binder dose. Since most of studies did not report dialysis dose nor measures of β_2-microglobulin clearance, it is unclear whether these improved clinical findings are due to increased treatment frequency or increased solute removal.

Since the publication of this SDHD systemic review, investigators from Texas have reported the results of a nonrandomized, controlled study of 26 patients on SDHD (six sessions per week, 3 hours per session) and 51 matched patients on conventional hemodialysis.[114] Unlike the results from the SDHD systematic review, significant decreases in serum phosphate and calcium-phosphate product were observed in this 12-month study. In a follow-up report, the authors hypothesize that the lack of effect of previous SDHD studies on mineral metabolism control is likely due to dialysis session length being less than 3 hours in duration in those studies.[115]

Additional evidence regarding patient outcomes treated by SDHD is expected in 2010 when results from the second Frequent Hemodialysis Network study should be availabel.[112] In this study patients are randomized to in-center SDHD (five to six sessions per week, less than 3 hours per session) or thrice weekly in-center conventional hemodialysis. Outcomes are similar to the NHD randomized trial described previously.

Dialysis Dose in More Frequent Treatments

The previous results suggest that certain patient outcomes are improved when hemodialysis treatments are performed more frequently than thrice weekly. Although it is assumed that the dialysis dose during SDHD is higher than conventional thrice-weekly hemodialysis, and it is readily apparent that dialysis dose during NHD is substantially higher, how patient outcomes are related to dialysis dose and/or fluid removal during frequent hemodialysis therapies is unclear. There is not enough clinical experience nor is there sufficient understanding of the pathophysiology of uremia to determine the minimum or optimal dose of dialysis when treatments are performed more than thrice weekly. It has been suggested that to achieve similar clinical outcomes, the weekly dose of dialysis when assessed as the sum of urea Kt/V values for all sessions in a week can be lower when

TABLE 22-1 Minimum Single-Pool Kt/V Values for Each Hemodialysis Session Corresponding to an stdKt/V of 2/Week

DIALYSIS SESSIONS	K_r<2 ml/min/1.73 m²	K_r>2 ml/min/1.73 m²
2 ×/week	Not recommended	2
3 ×/week	1.2	0.8
4 ×/week	0.8	0.6
6 ×/week	0.5	0.4

K_r denotes residual renal clearance of urea.

treatments are more frequent. Experimental evidence supporting this concept is however lacking; therefore, all such proposals for either the minimum or optimal dialysis dose during more frequent therapies must be considered provisional. One method for estimating the minimum dose of hemodialysis for treatments delivered more than thrice weekly uses the concept of urea standard Kt/V (stdKt/V) as described by Gotch.[116] This concept is based on the assumption that patient outcomes are similar during hemodialysis and peritoneal dialysis because their mean peak BUN concentrations are equal. Projecting this concept to more frequent hemodialysis, the minimum dose of daily hemodialysis has been proposed to be that which achieves a stdKt/V of 2, similar to that achieved during routine hemodialysis and peritoneal dialysis.[116]

This approach has been used to set K/DOQI clinical practice recommendations for the minimum dose of dialysis for hemodialysis therapy with different treatment schedules.[32] These minimum dose recommendations were calculated based on the concepts proposed by Gotch[116] and later modified for postdialysis rebound of urea by Leypoldt and colleagues[117] Table 22-1 lists minimum recommended spKt/V values for different treatment frequencies to achieve a stdKt/V of 2; these recommendations are dependent on residual renal clearance of urea. It should again be emphasized that clinical evidence behind these recommendations is lacking; they are based on a theoretical construct only. European Best Practice Guidelines recommend that dialysis dose should account for treatment frequency but allow reporting dose as weekly stdKt/V, solute removal index, or equivalent renal clearance.[33]

It is of interest to contrast these minimum target values with those to be used in the Frequent Hemodialysis Network in-center SDHD study.[112] In that study, the dialysis dose for six sessions per week requires a treatment time between 1.5 and 2.75 hours with an eKt/V(n) (where $V[n] = 3.271 \times V^{0.67}$) of 0.9 per session. The use of eKt/V(n) was to optimize study design issues unique to this study; it is not intended for clinical use. It was predicted[118] that median stdKt/V values in the SDHD arm of this study will be 3.75, substantially higher than the minimum required by the K/DOQI clinical practice recommendations.

Dose of Middle Molecule Clearance in More Frequent Treatments

Similar to urea, it is possible that the dose of middle molecule clearance requires modification when hemodialysis is applied more frequently than thrice weekly. The parameter chosen for evaluating middle molecule removal during the HEMO Study was the dialyzer clearance of β_2-microglobulin. This is an appropriate parameter for the middle molecule dose only if treatment times among the different groups are similar. When comparing therapies to widely varying weekly treatment times, however, the effect of treatment time will need to be taken into account. A potential dose parameter for middle molecule removal would be the product of dialyzer clearance of β_2-microglobulin times weekly treatment time, similar to the definition of dialysis dose for small solutes such as urea Kt. Whether this parameter should be normalized to body size is unclear.

The use of the product of dialyzer clearance of β_2-microglobulin times weekly treatment time to evaluate middle molecule dose would predict that therapies using the same dialyzer for the same total weekly treatment time, independent of treatment frequency, would be equivalent. Thus, SDHD treatments six times per week for one-half the conventional treatment time per session should have the same weekly dose of middle molecule clearance as thrice weekly treatments with the conventional treatment time per session. Data from a small crossover trial on SDHD are consistent with this concept because the change from conventional thrice-weekly HD to SDHD using this algorithm was shown to have no effect on predialysis serum β_2-microglobulin levels.[119] In contrast, the use of NHD where weekly treatment times are approximately four times those for conventional thrice-weekly hemodialysis should be associated with a substantially higher dose of middle molecule clearance. Data from the Toronto group have indeed demonstrated that use of NHD led to substantial reductions in predialysis serum β_2-microglobulin levels over time.[120] These relationships should hold largely independent of blood and dialysate flow rates during NHD and SDHD, because dialyzer clearance of β_2-microglobulin is relatively independent of these parameters within the ranges that are usually used in clinical HD.

A full list of references are available at www.expertconsult.com.

Chapter 23

HEMODIALYSIS-ASSOCIATED INFECTIONS

Matthew J. Arduino, M.S., Dr. P.H., Priti R. Patel, M.D., M.P.H., Nicola D. Thompson, Ph.D. and Martin S. Favero, Ph.D.

The findings and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Of the patients with end-stage renal disease (ESRD) treated by maintenance dialysis in the United States, approximately 92% are on maintenance hemodialysis.[1] Maintenance hemodialysis patients are at increased risk for infection because uremia is known to make patients with ESRD more susceptible to infectious agents through defects in cellular immunity, neutrophil function, and complement activation.[2,3] In addition, because the process requires vascular access for long periods in an environment where multiple patients receive hemodialysis concurrently, repeated opportunities exist for transmission of infectious agents. Patient-to-patient transmission of infectious agents, directly or indirectly through contaminated devices, equipment, supplies, injectable medications, environmental surfaces, or hands of healthcare personnel have all been demonstrated. Furthermore, hemodialysis patients require frequent hospitalizations and surgery, which increases their opportunities for exposure to healthcare-associated infections. This chapter describes 1) the major infectious diseases that can be acquired in the dialysis center setting, 2) important epidemiological and environmental microbiological considerations, and 3) infection control strategies.

MICROBIAL CONTAMINANTS IN HEMODIALYSIS SYSTEMS

Technical development and clinical use of hemodialysis delivery systems improved dramatically in the late 1960s and early 1970s. However, a number of microbiological parameters were not accounted for in the design of many hemodialysis machines and their respective water supply systems. There are many situations where certain types of gram negative water bacteria can persist and actively multiply in aqueous environments associated with hemodialysis equipment. This can result in the production of massive levels of gram negative bacteria, which can directly or indirectly affect patients by septicemia or endotoxemia.[4–17]

Gram negative water bacteria are commonly found in water supplies used for hemodialysis. Under certain circumstances, these microorganisms can persist and multiply in aqueous environments associated with hemodialysis equipment. These bacteria can adhere to surfaces and form biofilms (glycocalyces), which are virtually impossible to eradicate.[6,18–20] Control strategies are designed not to eradicate bacteria but to reduce their concentration to relatively low levels and to prevent their regrowth.

Although certain genera of gram negative water bacteria (e.g., *Burkholderia, Flavobacterium, Pseudomonas, Ralstonia, Serratia*, and *Sphingomonas*) are most commonly encountered,

virtually any bacterium that can grow in water can be a problem in a hemodialysis unit. Several species of nontuberculous mycobacteria may also contaminate water treatment systems, including *Mycobacterium chelonae, M. abscessus, M. fortuitum, M. gordonae, M. mucogenicum, M. scrofulaceum, M. kansasii, M. avium*, and *M. intracellulare*; these microorganisms do not contain bacterial endotoxin but are comparatively resistant to chemical germicides.[21–26]

Gram negative water bacteria can multiply even in water containing relatively small amounts of organic matter, such as water treated by distillation, softening, deionization, or reverse osmosis, reaching levels of 10^5 to 10^7 microorganisms/ml[6]; these levels are not associated with visible turbidity. When treated water is mixed with dialysis concentrate, the resulting dialysis fluid is a balanced salt solution and growth medium almost as rich in nutrients as conventional nutrient broth.[6,27] Gram negative water bacteria growing in dialysis fluids can reach levels of 10^8 to 10^9 microorganisms/ml producing visible turbidity.

Bacterial growth in water used for hemodialysis depends on the types of water treatment system used, dialysate distribution systems, dialysis machine type, and method of disinfection (Table 23-1).[6,18,21,28,29] Each component is discussed separately below.

Microbial Contamination of Water

Water used for the production of dialysis fluid must be treated to remove chemical and microbial contaminants. The Association for the Advancement of Medical Instrumentation (AAMI) has published guidelines and recommended practices for the chemical and microbial quality of water used to prepare dialysis fluid and reprocess hemodialyzers (Table 23-2).[30–32] Some components of the water treatment system may allow for amplification of water bacteria. For example ion exchangers such as water softeners and deionizers do not remove endotoxin or microorganisms and provide many sites for significant bacterial multiplication.[33] Granular activated carbon adsorption media (i.e., carbon filters) are used primarily to remove certain organic compounds and available chlorine (free and combined) from

TABLE 23-1 Factors Influencing Microbial Contamination in Hemodialysis Systems

FACTORS	COMMENTS
Water Supply (Water Source)	
Groundwater	Contains endotoxin and bacteria
Surface water	Contains high levels of endotoxin, bacteria, and other organisms
Water treatment at the dialysis center	
None	Not recommended
Filtration	
Prefilter	Particular filter to protect equipment; does not remove microorganisms
Absolute filter (depth or membrane)	Removes bacteria but unless changed frequently or disinfected, bacteria will accumulate and grow through the filter; acts as a significant reservoir of bacteria and endotoxin
Granular activated carbon (GAC)	Removes organics and available chlorine or chloramine; significant reservoir of water bacteria and endotoxin
Water treatment devices	
Ion-exchange (softener, deionization)	Softeners and deionizers remove cations and anions, contaminants from source water; significant reservoir for bacteria and endotoxin
Reverse osmosis	Removes bacteria, endotoxin, chemicals, and must be cleaned and disinfected; most systems used for dialysis applications operate under high pressure
Ultraviolet germicidal irradiator	Kills most bacteria, but there is no residual; some UV-resistant bacteria can develop
Ultrafilter	Removes bacteria and endotoxin; operates on normal line pressure; can be positioned distal to storage tank and deionizer; must be disinfected or changed
Water and dialysate distribution system	
Distribution pipes	
Size	Oversized diameters and length decrease fluid flow and increases bacterial reservoir in the form of biofilms for both treated water and central delivery systems (bicarbonate concentrate or bicarbonate dialysate)
Materials	Pipe materials influence bacterial colonization and biofilm formation and types of chemical disinfectants that can be used
Construction	Rough joints, dead ends, and unused branches can act as bacterial reservoirs
Elevation	Outlet taps should be located at highest elevation to prevent loss of disinfectant
Storage tanks	Generally undesirable because of large surface area and can act as a reservoir for water bacteria; a properly designed tank can minimize this risk
Dialysis machines	
Single-pass	Disinfectant should have contact time with all parts of the machine that are in contact with treated water or dialysate
Recirculating single-pass, or recirculating batch	Recirculating pumps and machine design allow for massive contamination levels if not properly disinfected; overnight disinfection has been recommended

TABLE 23-2 AAMI Microbial Quality Standards for Dialysis Fluids

	MICROBIAL BIOBURDEN		ENDOTOXIN	
TYPE OF FLUID	MAXIMUM CONTAMINANT LEVEL	ACTION LEVEL	MAXIMUM CONTAMINANT LEVEL	ACTION LEVEL
Water for all purposes	200 CFU/ml	50 CFU/ml	2 EU/ml	1 EU/ml
Conventional Dialysate	200 CFU/ml	50 CFU/ml	2 EU/ml	1 EU/ml
Ultrapure Dialysate	1 CFU/10 ml		0.03 EU/ml	
Dialysate for Infusion	1 CFU/1000 L*		0.03 EU/ml	

*Compliance with a maximum bacterial level of 10^{-6} CFU/ml cannot be demonstrated by culturing, but by processes developed by the machine manufacturers.

water, but they also significantly increase the level of water bacteria, yeast, fungi, and endotoxins.

A variety of filters are marketed to control bacterial contamination of water and dialysis fluids. Most are inadequate, especially if they are not routinely disinfected or frequently changed. Particulate filters, commonly called *"prefilters,"* operate by depth filtration and do not remove bacteria or endotoxin. These filters can become colonized with gram negative water bacteria, resulting in higher levels of bacteria and endotoxin in the filter effluent. Absolute filters, including membrane types, temporarily remove bacteria from passing water. However, some of these filters tend to clog, and gram negative water bacteria can "*grow through*" the filter matrix and colonize downstream surfaces of the filters within a few days. Further, absolute filters do not reduce levels of endotoxin in the effluent water. These filters should be changed regularly in accordance with the manufacturer's directions and disinfected in the same manner and at the same time as the rest of the water distribution system.

Ultraviolet germicidal irradiation (UVGI) is sometimes used to reduce microbial contamination in water, but the use of UVGI has some special considerations. The lamp should be appropriately sized for the flow rate of water passing through the device and the energy output should be monitored to insure effectiveness of the lamp. Manufacturers of the lamp may require routine replacement schedule. Some bacterial populations may develop resistance to UVGI. In recirculating dialysis distribution systems, repeated exposure to GUVI are used to ensure adequate disinfection; however, this approach allows for progressive removal of sensitive microorganisms and selection of UVGI-resistant organisms. In addition, bacterial endotoxins are not affected.

Reverse-osmosis is an effective water treatment modality that is used in more than 97% of U.S. hemodialysis centers. Reverse osmosis possess the singular advantage of being able to remove a variety of substances including microorganisms and endotoxin from supply water based primarily on particle size and adsorption to the membrane. However, low numbers of gram negative and acid fast organisms may penetrate the membrane or by other means (leaks around seals) and colonize downstream portions of the water distribution system. Consequently the reverse osmosis unit must be disinfected routinely.

We recommend a water treatment system that produces chemically adequate water while avoiding high levels of microbial contamination. The components in a typical water system should include 1) prefilters, 2) a water softener, 3) carbon adsorption tanks (at least two in series), 4) a particulate filter (to protect the reverse osmosis membrane), and 5) a reverse osmosis unit. If one includes a deionization unit as a polisher (post reverse osmosis unit) and a storage tank, the final component should be an ultrafilter to remove microorganisms and endotoxin. As the incoming tap water passes through the system components, it becomes more chemically pure, but the level of microbial contamination increases, which is why ultrafiltration and reverse osmosis are important. Additional components or processes may be included in the pretreatment chain (see Table 23-1) depending on the pH, potable water disinfectant, and the chemical quality of the incoming municipal water. If the system is adequately disinfected and properly maintained, the microbial content of water should be well within the recommended limits.

Distribution Systems

Water that has passed though the water distribution system (product water) is then distributed to individual dialysis machines, where it is combined with dialysate concentrates, and to a reprocessing area if a facility reprocesses hemodialyzers. It may also be combined with concentrates at a central location where the resulting dialysis fluid is supplied to the individual machines. Plastic pipe (most often polyvinyl chloride) is then used to distribute water, or dialysis fluids to the dialysis machines. Distribution systems should include the use of a loop based system and no dead ended pipes. Outlets to dialysis machines should have a relatively short path with the least amount of fittings and the use of valves with minimal dead space. Voids, dead ends, and large surface areas serve as sites for microbial colonization. Also large diameter pipes decrease fluid velocity and increase the wetted surface area available for microbial colonization. In addition, long pipe runs also increase the available surface area for colonization. Gram negative water bacteria in fluids remaining in pipes overnight can rapidly multiply and colonize wetted surfaces of the distribution system, producing microbial populations and endotoxin in quantities proportional to the total volume of the surface area. Such colonization results in the formation of protective biofilm, which is difficult to remove and protects the bacteria and other organisms from disinfection.[34]

Routine disinfection of the water or dialysate distribution system should be performed on a regular basis so that the microbial quality of the fluids is within the acceptable standards range. The frequency of disinfection may be at a minimum at least monthly.[27,35] However, AAMI standards and recommended practices are community consensus standards, and do not specify a schedule for disinfection other

than to suggest that routine disinfection be conducted. In many instances, microbiological monitoring can be used to determine the frequency of testing of disinfection of the distribution system.[35,36]

To prevent disinfectant draining from pipes by gravity before adequate contact time, distribution systems should be designed with all taps at equal elevation and at the highest point of the system. Furthermore, the system should be free of rough joints, dead end pipes, and taps. Fluid trapped in such stagnant areas can serve as reservoirs for bacteria and fungi that later contaminate the rest of the distribution system.[37]

Storage tanks greatly increase the volume of fluid and surface area of the distribution system. If used these should be designed with a conical shaped bottom so that water exits the storage tank at its lowest point (and allows the tank to be drained), fitted with a tight sealing lid, equipped with a spray head, and possess an air vent containing a bacteriological filter. If used the storage tanks should be routinely cleaned, disinfected, and drained. In order to remove biofilm, use of strong oxidizers may aid in stripping biofilm from surfaces; however, physical scrubbing of the inner surfaces of the tank may be necessary. When using a storage tank a ultrafilter should be incorporated before water is pumped into the distribution system.

Hemodialysis Machines

In the 1970s, most dialysis machines were of the recirculating or recirculating single-pass type; their design contributed to relatively high levels of gram negative bacterial contamination in dialysis fluid. Currently, virtually all dialysis machines in the United States are single-pass machines. Single-pass machines tend to respond to adequate cleaning and disinfection procedures and, in general, have lower levels of bacterial contamination than do recirculating machines. Levels of contamination in single-pass machines depend primarily on the microbiological quality of the incoming water and the method of machine disinfection.[6,35]

Disinfection of Hemodialysis Systems

Routine disinfection of isolated components of the dialysis system frequently produces inadequate results. Consequently, the total dialysis system (water treatment system, distribution system, and dialysis machine) should be included in the disinfection procedure.

Disinfection of dialysis systems usually use sodium hypochlorite solutions, hydrogen peroxide solutions, commercially available peracetic disinfectants, ozone, and in some systems hot water pasteurization. Sodium hypochlorite solutions are convenient and effective in most parts of the dialysis system when used at the manufacture's recommended concentrations. Also, the test for residual available chlorine to confirm adequate rinsing is simple and sensitive. However, because chlorine is corrosive, it is usually rinsed from the system after relatively short dwell time of 20–30 minutes. The rinse water invariably contains organisms that can multiply to significant levels, if the system is permitted to stand overnight.[27] Therefore, disinfection with chlorine-based disinfectants are best used before the start of the first patient treatment session rather than at the end of the day. In centers dialyzing patients in multiple shifts with either batch or recirculating hemodialysis machines, it may be reasonable to disinfect with chlorine-based disinfectants between shifts and with another disinfectant or process (e.g., peroxyacetic acid, heat) at the end of the day.

Aqueous formaldehyde, peroxyacetic acid, hydrogen peroxide, or glutaraldehyde solutions can produce good disinfection results.[18,38,39] These products are not as corrosive as hypochlorite solutions and can be allowed to dwell in the system for long periods of time when the system is not in operation. However, formaldehyde, which has good penetrating power, is considered an environmental hazard and potential carcinogen and has irritating qualities that may be objectionable to staff.[40] The U.S. Environmental Protection Agency (EPA) has also limited the amount of formaldehyde that can be discharged into the wastewater stream, which has drastically reduced the use of this chemical in the dialysis community as a disinfectant. Peroxyacetic acid and glutaraldehyde are commercially available and are designed for use with dialysis machines when used according to the manufacturers labeled instructions. Glutaraldehyde use is also limited because it is considered to be a sensitizer and may pose a risk to healthcare workers.

Some dialysis systems (both water treatment and distribution systems, some hemodialysis machines) use hot-water disinfection (pasteurization) for control of microbial contamination. In this type of system water is heated to >80°C (176°F), is passed through the water distribution system and hemodialysis machine, or is passed just through the hemodialysis machine at the end of the day. These systems are excellent for controlling microbial contamination.

Monitoring of Water and Dialysis Fluid

Microbiological and endotoxin standards for water and dialysis fluids (see Table 23-2)[30–32,36,41] were originally based on the results of culture assays performed during epidemiological investigations. There is increasing evidence that the microbial quality of hemodialysis fluids plays a role in the chronic inflammatory response syndrome, anemia management, slows loss of residual renal function, and improved serum albumins in dialysis patients.[42–56] Increasing data suggest that use of ultrapure water and dialysate would benefit maintenance dialysis patients. However, there have been no randomized controlled studies to evaluate and confirm these studies.

Water samples should be collected from a source as close as possible to where water enters the dialysate proportioning unit. In most cases this is at the tap (not from that hose connecting the tap to the dialysis machine) the dialysis station. Water samples should be collected at least monthly from several locations within the dialysis unit. Samples should also be collected after any modifications or maintenance have been made to the water treatment and distribution systems. Dialysate samples should be collected during or at the end of the dialysis treatment from a source close to where the dialysis fluid either enters or leaves the dialyzer. Dialysate samples should be collected at least monthly from a representative number of dialysis machines. Samples of water and dialysate should also be collected when pyrogenic reactions are suspected. If centers reprocess hemodialyzers for

reuse on the same patient, water used to prepare disinfectant and rinse dialyzers should also be assayed monthly.[30,32] The maximum contaminant levels are 200 CFU/ml and 2 EU/ml (see Table 23-2).[30–32]

Specimens should be assayed within 30 minutes of collection or refrigerated at 4°C and assayed within 24 hours of collection. Conventional laboratory methods such as the pour plate, spread plate, or membrane filter technique can be used. Calibrated loops should not be used because they sample a small volume and are inaccurate. Blood and chocolate agar media should not be used because the organisms have adapted to nutrient poor environments and thus require specific media designed for the recovery of organism from water. In addition, microorganisms that are found in bicarbonate dialysis fluids require a small amount of sodium chloride. Consequently, to cover both conditions needed, trypticase soy agar (soybean casein digest agar) is currently recommended; however, one may also use standard methods agar, plate count agar, and tryptase glucose yeast agar, along with commercially available samplers.[57,58] The assay should be quantitative, not qualitative, and a standard technique for enumeration should be used. Colonies should be counted after 48 hours of incubation at 36°C.[31,41,59,60] Total viable counts are the objective of plate counts. Endotoxin testing should be conducted using either *Limulus* amebocyte lysate assay either Gel-clot method or one of the kinetic methods.

In an outbreak investigation, the assay methods may need to be both qualitative and quantitative; also detection of nontuberculous mycobacteria and in some cases fungi in water or dialysate may be desirable. In such instances plates should be incubated for 5 to 14 days at both 36°C and 28°C-30°C.

DIALYSIS-ASSOCIATED PYROGENIC REACTIONS

Gram negative bacterial contamination of dialysis water or components of the dialysis system (water, dialysate, water used for reprocessing) can cause pyrogenic reactions. Pyrogenic reactions are defined as objective chills (visible rigors) or fever (oral temperature ≥37.8°C [100°F]) or both in a patient who was afebrile (oral temperature up to ≤37°C [98.6°F]) and had no signs or symptoms of an infection before the start of the dialysis treatment session.[61,62] Depending on the type of dialysis system and the level of contamination, fever and chills may start 1 to 5 hours after dialysis has been initiated. Other symptoms may include hypotension, headache, myalgia, nausea, and vomiting. Pyrogenic reactions can occur without bacteria; because presenting signs and symptoms cannot differentiate bacteremia from pyrogenic reactions, blood cultures are necessary.

During 1990–2002 an annual average of 20%-24% of the hemodialysis centers in the United States reported at least one pyrogenic reaction in the absence of septicemia in patient undergoing maintenance dialysis.[63–73] Pyrogenic reactions can result from passage of bacterial endotoxin (lipopolysaccharide [LPS]) or other substances in the dialysate across the dialyzer membrane[74–78] or the transmembrane stimulation of cytokine production in the patient's blood by endotoxin in the dialysate.[75,79–81] In other instances endotoxin can enter directly into the blood stream with fluids that are contaminated with gram negative bacteria.[82] The signs and symptoms of pyrogenic reactions without bacteremia generally abate within a few hours after the dialysis has been stopped. If gram negative sepsis is associated, fever and chills may persist, and hypotension is more refractory to therapy.[4,82]

When a pyrogenic reaction occurs, the following steps are usually recommended: 1) careful physical examination of the patient to rule out other causes of chills and fever (e.g., pneumonia, vascular access infection, urinary tract infection); 2) blood cultures, other diagnostic tests (e.g., chest radiograph), and other cultures as clinically indicated; 3) collection of dialysate from the dialyzer (downstream side) for quantitative and qualitative microbiological culture; and 4) recording of the incident in a log or other permanent record. Determining the cause of these episodes is important because they may be the first indication of a remedial problem.

The higher the level of bacteria and endotoxin in dialysis fluid, the higher the probability that the bacteria or their products will pass through the dialyzer membrane to produce bacteremia or stimulate cytokine production. In an outbreak of febrile reactions among patients undergoing hemodialysis, the attack rates were directly proportional to the level of microbial contamination in the dialysis fluid.[6] Prospective studies also demonstrated a lower pyrogenic reaction rate among patients when they underwent dialysis with dialysis fluid that had been filtered from which most bacteria had been removed, compared to patients who underwent dialysis fluid that was highly contaminated (mean 19,000 CFU/ml).[5,61,83]

Among nine outbreaks of bacteremia, fungemia, and pyrogenic reactions not related to dialyzer reuse investigated by the Centers for Disease Control and Prevention (CDC), inadequate disinfection of the water distribution system or dialysis machines was implicated in seven (Table 23-3).[4,9,37,84–88] The most recent outbreaks occurred at dialysis centers using dialysis machines that had a port (waste-handling option) that allowed disposal of the extracorporeal circuit priming fluids. One-way check valves in the waste-handling option had not been maintained, checked for competency, or disinfected as recommended, allowing backflow from the effluent dialysate path into and contamination of the port and the attached blood line.[86–88]

Hemodialysis Reuse

Since 1976 the percentage of maintenance dialysis centers in the United States that reported reuse of disposable hollow-fiber dialyzers had increased steadily; the largest increase (126%) occurred during the period between 1976 to 1982, from 18% to 43%, and highest percentage 82% was reported in 1997.[72] However, the percentage of facilities reporting reusing dialyzers had declined to 63% in 2002.[70] This decline was primarily driven by one of the large dialysis chains to discontinue using the practice of reuse and to use single-use dialyzers only.

In 1986, AAMI Standards for reprocessing hemodialyzers[89] was adopted by the United States Public Health Service (USPHS) and was incorporated into regulation by

TABLE 23-3 Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008

DESCRIPTION	CAUSE(S) OF OUTBREAK	CORRECTIVE MEASURE(S) RECOMMENDED	REFERENCE
BACTEREMIA, FUNGEMIA, OR PYROGENIC REACTIONS NOT RELATED TO DIALYZER REUSE			
Pyrogenic reactions in 49 patients	Untreated city water contained high levels of endotoxin	Install a reverse osmosis system	4
Pyrogenic reactions in 45 patients	Inadequate disinfection of the fluid distribution system	Increase disinfection frequency and contact time of the	37
Pyrogenic reactions in 14 patients; 2 bacteremia; 1 death	Reverse osmosis water storage tank contaminated with bacteria	Remove or properly maintain and disinfect the storage tank	28
Pyrogenic reactions in 6 patients; 7 bacteremias	Inadequate disinfection of water distribution system and dialysis machines; improper microbial assay procedure	Use correct microbial assay procedures; disinfect water treatment system and dialysis machines following manufacturer's recommended procedures	273
Bacteremia in 35 patients with CVCs	CVCs used as facilities primary vascular access; median duration of infected catheters was 311 days; improper aseptic techniques	Uses CVCs when only absolutely necessary for vascular access; use appropriate aseptic technique when inserting and performing routine catheter care	274
3 pyrogenic reactions and 10 bacteremias in patients treated on machines with a port for disposal of dialyzer priming fluid (waste handling option or WHO port)	Incompetent check valves allowing backflow of fluid from the waste side of the machine into attached blood tubing; bacterial contamination of the WHO	Routine disinfection and maintenance of the dialysis machine including the WHO; check competency of WHO before patient treatment	86
Bacteremia in 10 patients treated on Machines with WHO port	Incompetent backflow to allow backflow from dialysate effluent side of the machine in the WHO port and attached bloodlines	Routine maintenance, disinfection, and check for check valve competence of the WHO port	87
Outbreak of pyrogenic reactions and gram-negative bacteremia in 11 patients	Water distribution system and machines were not routinely disinfected according to manufacturer's recommendations. Water and dialysate samples were cultured using a calibrated loop and blood agar plates—results were always as no growth	Disinfect machines according to manufacturer's recommendations include reverse osmosis water distribution system in the weekly disinfection schedule; microbiological assay should be performed by membrane filtration or spread plate using Trypticase Soy agar	9
Phialemonium curvatum access infections in 4 dialysis patients; 2 of these patients died of systemic disease	Observations at the facility noted some irregularities in site prep for needle insertion. All affected patients had synthetic grafts. One environmental sample was positive for *P. curvatum* (condensate pan of HVAC serving the unit)	Review infection control practices clean and disinfect HVAC system where water accumulated. Perform surveillance on all patients	275
Phialemonium curvatum blood stream infections 2 patients	Water system and dialysis machines with WHO ports not routinely maintained; water system contained dead legs and lab used wrong assays	Conduct routine maintenance and disinfection of machines and WHO ports; redesign water system to eliminate dead legs; have a routine schedule for disinfection of the water system	88
BACTEREMIA/PYROGENIC REACTIONS RELATED TO DIALYZER REPROCESSING			
Mycobacterial infections in 27 patients	Inadequate concentration of dialyzer disinfectant	Increase formaldehyde concentration used to disinfect dialyzers to 4%	22
Mycobacterial infections in 5 high-flux dialysis patients; 2 deaths	Inadequate concentration of dialyzer disinfectant and inadequate disinfection of water treatment system	User higher concentration of Peracetic acid for reprocessing dialyzers and follow manufacturers labeled recommendations; increase frequency of disinfecting the water treatment system	276
Bacteremia in 6 patients	Inadequate concentration of dialyzer disinfectant; water used to reprocess dialyzers did not meet AAMI standards	Use AAMI quality water; insure proper germicide concentration in the dialyzer	CDC unpublished data
Bacteremia and pyrogenic reactions in 6 patients	Dialyzer disinfectant diluted to improper concentration	Use disinfectant at the manufacturers recommended dilution and verify concentration	60
Bacteremia and pyrogenic reactions in 6 patients	Inadequate mixing of dialyzer disinfectant	Thoroughly mix disinfectant and verify proper concentration	10
Bacteremia in 33 patients at 2 dialysis centers	Dialyzer disinfectant created holes in the dialyzer membrane	Change disinfectant (product was withdrawn from the market place by the manufacturer)	277,278

Bacteremia in 6 patients; all blood isolates had similar plasmid profiles	Dialyzers were contaminated during removal and cleaning of headers with gauze; staff not routinely changing gloves; dialyzers not reprocessed for several hours after disassembly and cleaning	Do not use gauze or similar material to remove clots from header; change gloves frequently; process dialyzers after rinsing and cleaning	279
Pyrogenic reactions in 3 high-flux dialysis patients	Dialyzer reprocessed with 2 disinfectants; water for reuse did not meet AAMI standards	Do not disinfect dialyzers with multiple germicides; more frequent disinfection of water treatment system and conduct routine environmental monitoring of water for reuse	280
Pyrogenic reactions in 14 high-flux dialysis patients; 1 death	Dialyzers rinsed with city (tap) water containing high levels of endotoxin; water used to reprocess dialyzers did not meet AAMI standards	Do not rinse or reprocess dialyzers with tap water; use AAMI quality water for rinsing and preparing dialyzer disinfectant	281
Pyrogenic reactions in 18 patients	Dialyzers rinsed with city (tap) water containing high levels of endotoxin; water used to reprocess dialyzers did not meet AAMI standards	Do not rinse or reprocess dialyzers with tap water; use AAMI quality water for rinsing and preparing dialyzer disinfectant	11
Pyrogenic reactions in 22 patients	Water for reuse did not meet AAMI standards; improper microbiological technique was used on samples collected for monthly monitoring	Use the recommended assay procedure for water analysis of water and dialysate; disinfect water distribution system	8
Bacteremia and Candidemia among patients in 7 dialysis units (MN and CA)	Dialyzers were not reprocessed in a timely manner; some dialyzer refrigerated for extended periods of time before reprocessing; company recently made changes to header cleaning protocol	Reprocess dialyzers as soon as possible; follow joint CDC and dialyzer reprocessing equipment and disinfectant manufacturer guidance for cleaning and disinfecting headers of dialyzer	CDC unpublished data
TRANSMISSION OF VIRAL AGENTS			
26 patients seroconvert to HBsAg+ during a 10 month period	Leakage of coil dialyzer membranes and use of recirculating bath dialysis machines	Separation of HBsAg+ patients and equipment from all other patients	162
19 patients and 1 staff member seroconvert to HBsAg+ during a 14 month period	No specific cause determined; false-positive HBsAg results caused some susceptible patients to be dialyzed with infected patients	Laboratory confirmation of HBsAg+ results; strict adherence to glove use and use of separate equipment for HBsAg+ patients	282
24 patients and 6 staff seroconverted to HBsAg+ during a 10 month period	Staff not wearing gloves; surfaces not properly disinfected; improper handling of needles/sharps resulting in many staff needlestick injuries	Separation of HBsAg+ patients and equipment from susceptible patients; proper precautions by staff (e.g., gloves; handling of needles and sharps)	162
13 patients 1 staff member seroconvert to HBsAg+ during a 1 month period	Extrinsic contamination of intravenous medication being prepared adjacent to an area where blood samples were handled	Separate medication preparation area from area where blood processing for diagnostic tests is performed	167
8 patients seroconverted to HBsAg+ during a 5 month period	Extrinsic contamination of multidose medication vial shared by HBsAg+ and HBsAg susceptible patients	No sharing of supplies, equipment, and medications between patients	(CDC, unpublished data)
7 patients seroconverted to HBsAg+ during a 3 month period	Same staff caring for HBsAg+ and HBsAg susceptible patients	Separation of HBsAg+ patients from other patients; same staff should not care for HBsAg+ and HBsAg− patients	164
8 patients seroconverted to HBs Ag+ during 1 month	Not consistently using external pressure transducer protectors; same staff members cared for both HBsAg+ patients and susceptible patients	Use external pressure transducer protectors and replace after each use; same staff members should not care for HBV infected and susceptible patients on the same shift	272
14 patients seroconvert to HBsAg+ during a 6-week period	Failure to review results of admission and monthly HBsAg testing; inconsistent handwashing and use of gloves; adjacent clean and contaminated areas; <20% of patients vaccinated	Proper infection control precautions for dialysis facilities; routine review of serological testing; hepatitis B vaccination of all patients	165
TRANSMISSION OF VIRAL AGENTS			
7 patients on the same seroconvert to HBsAg+ during a 2 month period	Same staff member cares for HBsAg+ and HBsAg- patients on the same shift; common medication and supply carts were moved between stations, and multidose vials were shared	Dedicated staff for HBsAg+ patients; no sharing of equipment or supplies between any patients; centralized medication and supply areas; hepatitis B vaccination of all patients	165

Continued

TABLE 23-3 Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008—cont'd

DESCRIPTION	CAUSE(S) OF OUTBREAK	CORRECTIVE MEASURE(S) RECOMMENDED	REFERENCE
4 patients to seroconverted HBsAg+ during a 2 month period	Transmission appeared to occur during hospitalization at an acute care facility; no patients vaccinated	Hepatitis B vaccination of all patients	165
11 patients seroconverted to HBsAg+ during a 3 month period	Staff, equipment, and supplies were shared between HBsAg+ and HBs- patients; no patients were vaccinated	Dedicated staff for HBsAg+; no sharing of medication or supplies between any patients; hepatitis B vaccination of all patients	165
2 patients convert to HBsAg+ during a 4 month period	Transmission appeared to occur during hospitalization at an acute care facility; same staff cared for HBsAg+ and HBV susceptible patients; no patients vaccinated	Hepatitis B vaccination of all patients; dedicated staff for the care of HBsAg+ patients; no sharing of supplies or medication between patients; hepatitis B vaccination of all patients	165
36 patients with liver enzyme elevations consistent with non-A, non-B hepatitis	Environmental contamination with blood	Use proper precautions (e.g., gloving of staff; environmental cleaning); monthly liver function tests (e.g., ALT)	283
35 patients with elevated liver enzymes consistent with non-A, non-B hepatitis during a 22-month period; 82% of probable cases were anti-HCV+	Inconsistent use of infection control precautions, especially hand washing	Strict compliance to aseptic technique and dialysis center precautions	284
HCV infection developed in 7/40 (17.5%) HCV susceptible patients; shift specific attack rates of 29%-36%	Multidose vials left on top of machine and used on multiple patients; routine cleaning and disinfection of surfaces and equipment between patients not routinely done; arterial line for draining prime draped into a bucket that was not routinely cleaned or disinfected between patients	Strict compliance with infection control precautions for all dialysis patients; routine HCV testing	227,228
HCV infection developed in 5/61 (8%) HCV susceptible patients	Sharing of equipment and supplies between chronically infected and susceptible patients; preparation of medications at the dialysis station; use of mobile supply cart; prime bucket not cleaned or disinfected between patients; gloves not routinely used; clean and contaminated areas not separated	Strict compliance with infection control precautions for all dialysis patients; CDC does not recommend separation of equipment/supplies between HCV-infected and susceptible patients	227,228
HCV infection developed in 3/23 (13%) HCV susceptible patients; shift specific attack rate of 27%	Supply carts moved between stations and contained both clean and blood-contaminated items; medications prepared in the same area used for disposal of used injection equipment	Strict compliance with infection control precautions for all dialysis patients	228
HCV infection developed in 7/52 (13%) HCV susceptible patients; shift specific attack rates 4%-21%	Medication cart moved between stations and contained both clean and blood contaminated items; single dose medication vials used for multiple patients; cleaning and disinfection of surfaces and equipment between patients not routinely done	Strict compliance with infection control precautions for all dialysis patients	228
HCV infection developed in 9/119 (7.6%) 90 (10%) HCV susceptible patients; attack rate 10%	Cleaning and disinfection of surfaces and equipment between patients not routinely done; gloves not routinely used; medications not stored in separate clean area	Strict compliance with infection control precautions for all dialysis patients; routine HCV testing	229

CVCs, central venous catheters.

the Centers for Medicare and Medicaid Services (CMS). In general, dialyzer reuse appears to be safe if performed according to strict and established protocols. In the United States, dialyzer reuse has not been associated with the transmission of blood-borne pathogens such as hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV).[90,91] However, the reprocessing of dialyzers has been associated with pyrogenic reactions.[90] These adverse events may be the result of the use of incorrect concentrations of chemical germicides or the failure to maintain appropriate

water quality. Manual reprocessing of dialyzers that does not include a testing for membrane integrity, such as a pressure-leak test, may fail to detect membrane defects and may be a cause of both pyrogenic reactions and bacteremia.[90,91]

Some procedures used to reprocess hemodialyzers generally constitute high-level disinfection rather than sterilization.[20,92] There are several liquid chemical germicides that have been used to for high-level disinfection of dialyzers. Formaldehyde is a chemical solution from chemical supply houses and is not specifically formulated for dialyzer disinfection. There are commercially available chemical germicides specifically formulated for this purpose (e.g., peroxyacetic acid, chlorine-based, and glutaraldehyde-based products that are approved by the U.S. Food and Drug Administration (FDA) as sterilants or high-level disinfectants for reprocessing hemodialyzers. During the period between 1983 and 2002, the percentage of centers using formaldehyde for reprocessing dialyzers decreased from 94% to 20%, whereas the percentage using peroxyacetic acid increased from 5% to 72%. Only a minority of facilities (4%) reported using either glutaraldehyde or heat disinfection.[70]

In 1983 most centers used 2% aqueous formaldehyde with a contact time of approximately 36 hours to disinfect dialyzers.[93] In 1982 a dialysis center using this regimen experienced an outbreak of infections caused by nontuberculous mycobacteria.[22] It was subsequently shown that the 2% formaldehyde regimen was not effective against nontuberculous mycobacteria. Rather, a regimen of 4% formaldehyde with a minimum contact time of 24 hours was required to inactive high numbers of these organisms and was recommended as the minimum solution for reprocessing dialyzers.[20,90,92] A similar outbreak of systemic mycobacterial infections in five hemodialysis patients, resulting in two deaths, occurred when high-flux dialyzers were contaminated with *Mycobacterium abscessus* during manual reprocessing and disinfected with a commercial disinfectant prepared at a concentration that did not ensure complete inactivation of mycobacteria.[23] These two outbreaks of infections in dialysis patients emphasize the need to use dialyzer disinfectants at concentrations that are effective against more chemically resistant microorganisms, such as mycobacteria.

Outbreaks of pyrogenic reactions have often resulted in reprocessing hemodialyzers with water that did not meet AAMI standards (see Table 23-3). In most instances, the water used to rinse dialyzers or to prepare the dialyzer disinfectants exceeded the allowable AAMI microbial or endotoxin standards because the water distribution system was not disinfected frequently, the disinfectant was improperly prepared, or routine microbial assays were improperly performed.

High-Flux Dialysis and Bicarbonate Dialysate

High-flux dialysis uses dialyzer membranes and hydraulic permeability that are 5 to 10 times greater than conventional dialyzer membranes. There has been concern that bacteria or more likely endotoxin in the dialysate may penetrate these highly permeable membranes.

Another concern is that high-flux membranes require the use of bicarbonate rather than acetate dialysate. Acetate dialysate is prepared from a single concentrate with a high salt molarity (4.8M) that does not support the growth of most bacteria. Bicarbonate dialysate, however, must be prepared from two concentrates, an acid concentrate (acetic acid) with a pH of 2.8 that is not conducive to microbial growth and a bicarbonate concentrate with a relatively neutral pH and a salt molarity of 1.2M. Because the bicarbonate concentrate will support rapid growth,[60] its use can increase microbial and endotoxin concentrations in the dialysate and theoretically may contribute to an increase in pyrogenic reactions, especially when used during high-flux dialysis.

Some of the concern appeared justified by results of surveillance data during the 1990s, showing a significant association between use of high-flux dialysis and reporting of pyrogenic reactions among patients during dialysis.[94] However, a prospective study of pyrogenic reactions in patients receiving more than 27,000 conventional, high-efficiency, or high-flux dialysis with bicarbonate dialysate containing high concentrations of bacteria and endotoxin found no association between pyrogenic reactions and the type of dialysis treatment.[5] Although there seems to be conflicting data on the relationship between high-flux dialysis and pyrogenic reactions, centers providing high-flux dialysis should ensure that dialysate meets AAMI microbial standards (see Table 23-2).

OTHER BACTERIAL AND FUNGAL INFECTIONS

The annual adjusted mortality rates among hemodialysis patients are between 202.5 and 224.5 per thousand patient years at risk. Death as a result of infection is the second leading cause of mortality in this patient population (32.7/1000 patient years at risk) of which septicemia is the leading cause of infectious mortality.[1] In a number of published studies that have evaluated bacterial infections in outpatient hemodialysis, bacteremia occurred in 0.6% to 1.7% of patients per month and vascular access infections (with or without bacteremia) in 1.3% to 7.2% of patients per month.[95–105] A review of four studies published during 2002 estimated that 1.8% of hemodialysis patients have vascular access associated bacteremia each month, amounting to 50,000 cases nationally per year.[106]

Because of the importance of bacterial infections in hemodialysis patients, the CDC initiated a voluntary ongoing surveillance project in 1999.[104] All U.S. maintenance hemodialysis centers are eligible to enroll. Only bacterial infections associated with hospital admission or intravenous antimicrobial receipt are counted; because infections treated with outpatient oral antimicrobials are excluded, this system likely only detects more severe infections. During 1999–2001, 109 dialysis centers had reported data. Rates per 100 patient months were 3.2 for all vascular access infections (including access infections both with and without bacteremia), 1.8 for vascular access associated bacteremia, 1.3 for wound infections not related to the vascular access, 0.8 for pneumonias, and 0.3 for urinary tract infection. Among patients with fistulas or grafts, wounds were the most common site for infection. Among patients with hemodialysis catheters, infections of the vascular access site were the most common site for infection.[104]

In a study of 27 French hemodialysis centers, 28% of 230 infections in hemodialysis patients involved the vascular access, whereas 25% involved the lung, 23% the urinary tract, 9% the skin and soft tissues, and 15% other or unknown sites.[101] Thirty-three percent of infections involved either the vascular access site or were bacteremia of unknown origin, many of which might have been caused by occult access infection. Thus the vascular access site was the most common site for infection but accounted for only one-third of infections.

Bacterial pathogens causing infection can either be exogenous (i.e., acquired from contaminated dialysis fluids or equipment) or endogenous (i.e., caused by invasion of bacteria present in or on the patient). Exogenous pathogens have caused numerous outbreaks, most of which resulted from inadequate dialyzer reprocessing procedures (e.g., contaminated water or inadequate disinfectant concentration) or inadequate disinfection and maintenance of the water treatment and distribution system. During 1995 to 2006, five outbreaks were traced to contamination of the waste handling option on one type of dialysis machine.[86–88,107–109] Recommendations to prevent such outbreaks are published elsewhere.[110]

Contaminated medication vials are also a source of bacterial infection for patients. In 1999, an outbreak of *Serratia liquefaciens* bloodstream infections and pyrogenic reactions among hemodialysis patients was traced to contamination of vials of erythropoietin. These vials, which were intended for single use, were contaminated by repeated puncture to obtain additional doses and by pooling of residual medication into a common vial.[111]

Vascular Access Infections

Access site infections are particularly important because they can cause disseminated bacteremia or loss of the vascular access. Local signs of vascular access infection include erythema, warmth, induration, swelling, tenderness, breakdown of skin, loculated fluid, or purulent exudates.[98,99,104,112] In the CDC surveillance project, the initial reported rates of access associated bacteremia per 100 patient months were 1.8 overall and varied by access type: 0.25 for fistulas, 0.53 for grafts, 4.8 for permanent (tunneled, cuffed) catheters (tunneled, cuffed), and 8.7 for temporary (nontunneled, noncuffed) catheters.[104] A more recent summary of the data collected through this surveillance system (1995–2005) reported that the overall vascular access rate was 3.1 per 100 patient-months and varied from 0.6 for fistulas to 10.1 for temporary catheters.[113]

Vascular access infections are caused (in descending order of frequency) by *Staphylococcus aureus* (32%-53% of cases), coagulase negative staphylococci (CNS: 20%-32% of cases), gram-negative bacilli (10%-18%), other gram positive cocci (including enterococci; 10%-12%), and fungi (<1%).[104,114] The proportion of infections caused by *S. aureus* is higher among patients with fistulas or grafts, and the proportion caused by CNS is higher among patients dialyzed through catheters.

The primary risk factor for access related infection is access type, with catheters having highest risk for infection; grafts intermediate; and native arteriovenous (AV) fistulas the lowest.[97,98,102,113,114] Other potential risk factors for vascular access infection include 1) location of the access in the lower extremity; 2) recent vascular access surgery; 3) trauma, hematoma, dermatitis, or scratching over the access site; 4) poor patient hygiene; 5) poor needle insertion technique; 6) older age; 7) diabetes; 8) immunosuppression; 9) iron overload; 10) intravenous drug use; and 11) the chronic inflammatory state.[98,99,115–120]

Based on relative risk of both infectious and noninfectious complications, it is recommended that native AV fistulas be used more commonly and hemodialysis catheters less commonly; a goal of no more than 10% of patients maintained with permanent catheter-based hemodialysis treatment is recommended.[121–125] To minimize infectious complications, patients should be referred early for creation of an implanted access, thereby decreasing the time dialyzed through a temporary catheter. Additionally, catheters should be used only in patients for whom a permanent access is impossible. During the period between 1995 and 2002, the percentage of patients dialyzed through fistulas increased from 22% to 33% with most of the increase occurring after 1999.[70] During the same period, use of grafts decreased from 65% to 42%, and the use of catheters increased from 13% to 33%. However, data from CMS's ESRD Clinical Performance Measures (CPM) project indicate that 75% of new dialysis patient begin dialysis using a hemodialysis catheter; in 2006, 93.1% of patients with no pre-ESRD nephrologist care started dialysis with a catheter, whereas 76.9% of patients who had seen a nephrologist for 1 year or less and 65.2% of patients who saw a nephrologist for 1 year or more started dialysis with a catheter.[1]

Recommendations for preventing vascular access infections have been developed by the National Kidney Foundation[121–125] and the CDC.[126] Selected recommendations for preventing hemodialysis-catheter associated infections include: 1) not using antimicrobial prophylaxis before insertion or during use of the catheter; 2) not routinely replacing the catheter; 3) using sterile technique (cap, mask, sterile gown, large sterile drapes, and gloves) during catheter insertion; 4) limiting use of noncuffed catheters to 3 to 4 weeks; 5) using the catheter solely for hemodialysis unless there is no other alternative; 6) restricting catheter manipulation and dressing changes to trained personnel; 7) replacing catheter site dressing at each dialysis session or if damp, loose or soiled; 8) disinfecting skin before catheter insertion and dressing changes (a 2% chlorhexidine-based preparation is preferred); and 9) ensuring catheter-site care is compatible with catheter material.[126,127]

There have been a number of studies looking at the use of various antimicrobial locks to prevent catheter-related bloodstream infection among hemodialysis patients. Two recent meta analyses of these studies concluded that: 1) antimicrobial catheter lock solutions reduce catheter-related bloodstream infections, and the 2) use of these lock solutions should be considered in routine clinical practice in conjunction with other prevention modalities.[128,129] However, the long-term consequence of using antibiotics routinely in catheter locking solutions is unknown. Although results of these studies appear to be promising, CDC does not recommend the routine use of antimicrobial lock solutions for hemodialysis catheters because antimicrobial use can lead to antimicrobial resistance.[126,130]

In hemodialysis patients, the Infectious Disease Society of America has recommended treatment with nasal mupirocin in documented *S. aureus* carriers who have catheter-related blood stream infection with *S. aureus* and continue to need a hemodialysis catheter.[131,132] Otherwise the routine use of nasal mupirocin in patients with hemodialysis catheters is not recommended by either CDC or the National Kidney Foundation.[121,122,126]

Pneumonia

Hospital admissions for pneumonia have been declining overall for dialysis patients, however, pneumonia rates for hemodialysis patients are 1.8–2 times that of transplant recipients or peritoneal dialysis patients. Hospital admissions for pneumonia are also 102% higher among hemodialysis patients when compared to the general population.[1] In one study of a group of 433 dialysis patients over a 9 year period, pneumonia was the third most common cause of infection (following vascular access infections, and infections below the knee) and accounted for 13% of all infections.[133] One and 5 year survival probabilities are 0.55 and 0.17, respectively. Pneumonia is common among hemodialysis patients, carries a poor prognosis, and is often the antecedent to cardiovascular death.[134,135] A recent analysis of incident hemodialysis patients found pneumonia to be associated with chronic obstructive pulmonary disease, inability to transfer or ambulate, hemodialysis as initial therapy, advanced age ($\geq$75 years), and body mass index $\geq$30 kg/m.[135]

Antimicrobial Resistant Bacteria

Hemodialysis patients have been in the forefront of the epidemic of antimicrobial resistance, especially vancomycin resistance. One of the earliest reports of vancomycin-resistant enterococci (VRE) was from a renal unit in London, England, in 1988.[136] The prevalence of VRE stool colonization among dialysis patients has varied from 1.5% among pediatric dialysis patients in the UK[137] and 2.4% of adult dialysis patients at three dialysis centers in Indianapolis, IN[138] to 9.5% at a University hospital in Baltimore, MD.[139] In one center with a VRE prevalence of 9% these colonized patients developed VRE infections in 1 year.[140] It appears that hospital acquisition of VRE contributes substantially to the increasing prevalence of VRE in the chronic hemodialysis patient population.[141] Among enterococci causing blood stream infections in hemodialysis patients, up to 5% have been reported to be resistant to vancomycin.[104,142,143]

Vancomycin resistance in staphylococci has also been reported in dialysis patients. Five of the first six U.S. patients with infections associated with vancomycin intermediate-resistant *S. aureus* were receiving either peritoneal dialysis or hemodialysis.[144,145] Additionally, the first patient found to be with a fully resistant *S. aureus* (VRSA) strain was a maintenance dialysis patient; the VRSA was isolated from a diabetic foot wound and from a temporary catheter exit site.[146] In the period between 2002 and 2009 there have been a total of nine cases of VRSA in the United States; three of these cases had chronic renal failure and two were hemodialysis patients.[147,148] Five of the seven VRSA cases occurred in southeastern Michigan and contained a plasmid carrying the vanA gene, which had been donated from a VRE donor.[149]

The percent of hemodialysis facilities reporting Methicillin-resistant *Staphylococcus aureus* (MRSA) infection or colonization among has increased from 40% in 1995[71] to 76% in 2002.[70] In a recent CDC study assessing the incidence of invasive MRSA infection among dialysis patients, the incidence of invasive MRSA infection was found to be 42.5 cases/1000 population.[150] This is 100-fold higher than the general population, where rates for invasive MRSA infection are 0.2–0.4 cases/1000 population. Additionally, a study in the United Kingdom of vascular access infections found that MRSA was responsible for 30% of all catheter-related infections.[151]

In order to combat emerging antimicrobial resistance in dialysis patients, one must understand the transmission kinetics involved with each organism. For certain patients, including those infected with MRSA or VRE, Contact Precautions are used in the hospital setting.[152] However, Contact Precautions are not recommended in hemodialysis centers for patients infected or colonized with pathogenic bacteria for several reasons. First, although contact transmission of pathogenic bacteria is well-documented in hospitals, similar transmission has not been well-documented in hemodialysis centers and at least one study has demonstrated that the majority of transmission and acquisition of pathogens occurs when these patients are admitted to the acute care setting.[141] Transmission of pathogenic bacteria might not be apparent in dialysis centers, possibly because it occurs less frequently than in the acute care setting or results in undetected colonization rather than overt infection. Also because dialysis patients are frequently hospitalized, determining whether transmission occurred in either the outpatient or inpatient setting may be difficult. Second, contamination of the patient's skin, bedclothes, and environmental surfaces with pathogenic bacteria is likely to be more common in hospitals (where patients spend 24 hours a day) than in an outpatient maintenance dialysis center (where patients may spend up to 9–15 hours per week). Third, the routine use of infection control practices recommended for hemodialysis facilities, which are more stringent than the Standard Precautions routinely used in hospitals, should prevent transmission.

HEPATITIS B VIRUS

Hepatitis B virus (HBV) is the most efficiently transmitted pathogen in the dialysis setting. Recommendations for control of hepatitis B in hemodialysis setting were first published in 1977,[153] and by 1980 their widespread implementation was associated with a sharp decrease in the incidence of HBV infection among both patients and staff members.[154,155] In 1982, the hepatitis B vaccine was recommended for all susceptible patients and staff members.[156] However, after these recommendations were made both outbreaks and new acquisition of hepatitis B infection continues to have occurred among susceptible maintenance hemodialysis patients in the United States. Hepatitis A and E viruses, which are spread by the fecal-oral route and rarely by blood, have not been associated with hemodialysis.

Epidemiology

During the early 1970s, HBV infection was endemic in maintenance hemodialysis units and outbreaks were common. Subsequently, the incidence and prevalence of HBV infection among maintenance hemodialysis patients in the United States has declined dramatically, and by 2002, was 0.12% and 1%, respectively.[70] Newly acquired HBV infections were reported by 2.8% of U.S. hemodialysis centers, and 27.3% of centers reported one or more patients with chronically infected patients.[70]

The chronically infected patient is central to the epidemiology of HBV transmission. HBV is transmitted by percutaneous (i.e., puncture through the skin) or per mucosal (direct contact with mucus membranes) exposure to infectious blood or body fluids that contain blood. All hepatitis B surface antigen (HBsAg)-positive persons who are also positive for hepatitis B e antigen (HBeAg) have an extraordinary level of HBV circulating in their blood, approximately 10^8 to 10^9 virions per milliliter.[157,158] With virus titers this high in blood, body fluids containing serum or blood may also contain high levels of HBV and are potentially infectious. Furthermore, HBV at titers of 10^2–10^3 virions/ml can be present on environmental surfaces in the absence of any visible blood and still cause infection.[157,159–161]

HBV is relatively stable in the environment and has been shown to remain viable for at least 7 days on environmental surfaces at room temperature.[157,159,161] HBsAg has been detected in dialysis facilities on hemostats, scissors, dialysis machine control panels, and door knobs.[161] Thus blood-contaminated surfaces that are not routinely cleaned and disinfected represent a reservoir for HBV transmission. Dialysis staff members can transfer virus to susceptible patients from surfaces in the absence of visible blood and still cause infection.[157,159,161]

Most HBV outbreaks among hemodialysis patients (see Table 23-3) were caused by cross-contamination to patients through 1) environmental surfaces, supplies (e.g., hemostats, clamps), or equipment that were not routinely clean and disinfected after each use; 2) multiple-dose vials or intravenous solutions that were not used exclusively for one patient; 3) medications for injections that were prepared adjacent to areas where blood samples were handled; and 4) staff members who simultaneously provided care for both infected (HBsAg-positive) patients and susceptible patients.[82,162–168] Once the factors that promote HBV transmission among hemodialysis patients were identified, recommendations for control were published in 1977.[153] These recommendations included: 1) serological screening of patients (and staff members) for HBV infection, including monthly testing of all susceptible patients for HBsAg; 2) isolation of all HBsAg-positive patients in a separate room; 3) assignment of staff members to HBsAg-positive patients and not to HBV susceptible patients during the same shift; 4) assignment of dialysis equipment to HBsAg-positive patients that is not shared with HBV susceptible patients; 5) assignment of a supply tray to each patient (regardless of serological status); 6) cleaning and disinfection of nondisposable items (e.g., hemostats, clamps, scissors) before use on another patient; 7) glove use whenever patient or hemodialysis equipment is touched and glove changes between each patient (and station); and 8) routine cleaning and disinfection of equipment and environmental surfaces.

The segregation of HBsAg-positive patients and their equipment from HBV-susceptible patients resulted in 70% to 80% reduction in the incidence of HBV infections among hemodialysis patients.[155,169,170] The success of isolation practices in preventing transmission of HBV infection is linked to other infection control practices, including routine serological surveillance and routine cleaning and disinfection. Frequent serological testing for HBsAg detects patients recently infected with HBV so isolation procedures can be implemented before cross-contamination can occur. Environmental control by routine cleaning and disinfection procedures reduces the opportunity for cross contamination, either directly from environmental surfaces or indirectly by hands of personnel.

Despite the low incidence of HBV infection among hemodialysis patients, outside the United States, have outbreaks continued to occur in maintenance hemodialysis centers.[171–175] Investigations of these outbreaks have documented failures to use recommended infection control practices, including: 1) failure to routinely screen patients for HBsAg or routinely review results of testing to identify infected patients; 2) assignment of staff members to the simultaneous care of both infected and susceptible patients; and 3) sharing of supplies, particularly multidose medication vials, among patients.[165] In addition, in the United States only about 56% percent of patients have received the hepatitis B vaccine.[70] National surveillance data have demonstrated independent risk factors among maintenance hemodialysis patients for acquiring HBV infection include the presence of $\geq$1 HBV-infected patient in the hemodialysis facility who was not isolated and a vaccination rate $<$50% among patients.[63]

HBV infection among maintenance hemodialysis patients has also been associated with hemodialysis provided in the acute care setting.[165,168] Transmission appeared to stem from chronically HBV infected patients who shared staff members, multiple-dose medication vials, and other supplies and equipment with susceptible patients. These episodes were recognized only after the patients had returned to their outpatient dialysis facilities, and routine HBsAg testing was resumed. Transmission from HBV infected maintenance hemodialysis patients to patients undergoing hemodialysis procedures for acute renal failure has not been documented, possibly because these patients are dialyzed for short durations and have limited exposure. However, such transmission could go unrecognized because acute renal failure patients are unlikely to be tested for HBV infection.

Other risk factors for acquiring HBV infection include injection drug use, sexual and household exposure to HBV infected contacts, exposure to multiple sexual partners, male homosexual activity, and perinatal exposure. Dialysis patients should be educated about these and other risks and, for those patients with active HBV infection (HBsAg positive), informed that their sexual partners and household contacts should be vaccinated.[176–178]

Screening and Diagnostic Tests

Several well-defined antigen-antibody systems are associated with HBV infection, including HBSAg and antibody to HBsAg (anti-HBs); hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B early antigen (HBeAg) and antibody to HBeAg (anti-HBe). Serological

TABLE 23-4 Interpretation of Serological Test Results for Hepatitis B Virus Infection

SEROLOGICAL MARKERS				INTERPRETATION
HBsAg[a]	TOTAL ANTI-HBc[b]	IgM[c] ANTI-HBc	ANTI-HBs[d,e]	
−	−	−	−	Susceptible, never infected
+	−	−	−	Acute infection, early incubation[e]
+	+	+	−	Acute infection
−	+	+	−	Acute resolving infection
−	+	−	+	Past infection, recovered and immune
+	+	−	−	Chronic infection
−	+	−	−	False positive (i.e., susceptible), past infection, or low-level chronic
−	−	−	+	Immune if titer ≥10 mIU/ml

[a]Hepatitis B surface antigen.
[b]Antibody to hepatitis B core antigen.
[c]Immunoglobulin M.
[d]Antibody to hepatitis B surface antigen.
[e]Transient HBsAg positivity (lasting ≤18 days) might be detected in some patients during vaccination.

assays are commercially available for all of these except for HBcAg because no free HBcAg circulates in the blood. One or more of these serological markers are present during different phases of HBV infection (Table 23-4).[179] HBV infection can also be detected, using qualitative or quantitative tests for HBV DNA.[180,181] These tests are most commonly used for HBV infected patients being managed with antiviral therapy.[182–186]

The presence of HBsAg is indicative of ongoing HBV infection. In newly infected individuals, HBsAg is present in serum 30–60 days after exposure to HBV and persists for variable periods.[176] Transient HBsAg positivity (lasting <18 days) can be detected in some patients during vaccination and is clinically insignificant.[176,187,188] Anti-HBc develops in all HBV infections, appearing at the onset of symptoms or liver test abnormalities in acute HBV infection, rising to rapidly to high levels, and persisting for life. Acute or recently acquired infection can be distinguished by presence of the immunoglobulin M (IgM) class of anti-HBc, which persists for approximately 6 months.

In individuals who recover from HBV infection, HBsAg is eliminated from the blood, and anti-HBs develops during convalescence, usually within 3–4 months. The persistence of anti-HBs indicates immunity from HBV infection. After recovery from natural infection, most individuals will be positive for both Anti-HBc and anti-HBs, whereas only anti-HBs develops in patients who are successfully vaccinated against hepatitis B. Individuals who do not recover from HBV infection and become chronically infected remain HBsAg-positive (and anti-HBc positive), although a small proportion of patients (0.5-2.0%) eventually clear HBsAg and might usually develop anti-HBs.[177,189]

In some individuals, the only HBV serological marker detected is anti-HBc (i.e., isolated anti-HBc). Among most asymptomatic persons in the United States tested for HBV infection, an average of 2% (range: <0.1%-6%) test positive for anti-HBc;[188] among injecting drug users, however, the rate is 24%-28%.[189,190] In general the frequency of isolated anti-HBc is directly related to the frequency of previous HBV infection in the population and can have several explanations.[177,188–190] This pattern can occur after HBV infection among individuals who have recovered but whose anti-HBs have waned or among individuals who have failed to develop anti-HBs. Individuals in the latter category include those who circulate HBsAg at levels not detected by commercial serological assays (low-level chronic HBV infection). However, HBV DNA has been detected in <10% of these individuals with isolated anti-HBc, and these individuals are unlikely to be infectious to others except under unusual circumstances involving direct percutaneous exposures to large quantities of blood (e.g., transfusion).[193–195] In most persons with isolated anti-HBc, the result appears to be false positive. Data from several studies have demonstrated that a primary anti-HBs response develops in most of these individuals after a three dose series of hepatitis B vaccine.[196,197] No data exist on response to vaccination among hemodialysis patients with this serological pattern.

A third antigen, HBeAg, can be detected in the serum of individuals with acute or chronic HBV infection. The presence of HBeAg correlates with viral replication and high levels of virus (i.e., high infectivitiy). Anti-HBe correlates with loss of replicating virus and with lower levels of virus. However, all HBsAg-positive patients should be considered potentially infectious, regardless of their HBeAg or anti-HBe status.

HEPATITIS C VIRUS

Hepatitis C virus (HCV) is a single-stranded RNA virus that belongs to the family *Flaviviridae*.[198] HCV was first recognized as non-A, non-B hepatitis virus (NANBH) in 1974 until cloning of the etiological agent in 1989.[199–201] HCV is another efficiently transmitted bloodborne viral pathogen in the dialysis setting. It is not as efficiently transmitted as HBV in this setting, and recommended infection control practices do prevent transmission among hemodialysis patients.[152,202–204] However, both outbreaks and new acquisition of HCV infection continue to occur among maintenance hemodialysis patients.

Epidemiology

Data are limited on the current incidence and prevalence of HCV infection among maintenance hemodialysis patients. In the United States 2002, 63% of dialysis centers tested patients for anti-HCV. In the facilities that tested, the incidence rate in 2002 was 0.34%, and among the centers that tested for anti-HCV, the prevalence of anti-HCV among patients was 7.8%, a decrease of 25.7% since 1995.[70] Only 11.5% of dialysis facilities reported newly acquired HCV infection among their patients. Higher incidence rates have been reported from cohort studies of dialysis patients in the United States (<1% to 3%), Japan (<2%), and Europe (3% to 15%).[205–211] Higher prevalence rates (10% to 85%) also have been reported in individual facilities and other sites.[208,212–216]

HCV is moderately stable in the environment and can survive drying and environmental exposure to room temperature for at least 16 hours.[217] HCV is most efficiently transmitted by direct percutaneous exposure to blood, and like HBV, the chronically infected patient is central to the epidemiology of HCV transmission. Risk factors associated with HCV infection among hemodialysis patients include blood transfusions from unscreened donors, intravenous drug abuse, low staff to patient ratios, and years on dialysis.[205,211,218–222] The number of years on dialysis is the major risk factor that is independently associated with higher rates of HCV infection. As the time patients spent on dialysis increased, their prevalence of HCV infection increased from an average of 12% for patients receiving dialysis <5 years to an average of 37% for patients receiving dialysis >5 years.[205,222–226]

These studies and investigations of dialysis-associated outbreaks of HCV infection indicate that HCV transmission most likely occurs because of inadequate infection control practices.[227–229] During 1998 to 2008, CDC investigated five outbreaks of HCV infection among patients in chronic hemodialysis centers.[228,229] In four of the outbreaks, multiple transmissions of HCV occurred during periods ranging from 6 months to 7 years (attack rates: 8%-17.5%), and seroconversions were associated with receiving dialysis immediately after or at machine adjacent to a chronically infected patient. Multiple opportunities for cross-contamination among patients were observed, including: 1) equipment and supplies that were not disinfected between patient use; 2) use of common medication carts to prepare and distribute medications at patient stations; 3) sharing of multiple dose vials, which were placed at patients' stations on the top of the hemodialysis machine; 4) contaminated priming buckets that were not routinely changed or cleaned and disinfected between patients; 5) machine surfaces that were not routinely cleaned and disinfected between patients; and 6) blood spills that were not cleaned up promptly. In another outbreak, there were multiple infections clustered at one point in time (shift specific attack rate of 27%), suggesting a common exposure event. Multiple opportunities for cross-contamination from chronically infected patients also were observed in this unit. In particular, supply carts were moved from station to station and contained both clean supplies and blood contaminated items, including small biohazard containers, sharps disposal boxes, and used Vacutainers® containing patients' blood.

Other reported risk factors for acquiring HCV include injection drug use, receipt of unscreened blood via transfusion, exposure to an HCV-infected sexual partner or household contact, multiple sexual partners, and perinatal exposure.[230,231] The efficiency of transmission in settings involving sexual or household exposure to infected contacts is low, and the magnitude of risk and the circumstances under which these exposures result in transmission are not well-defined.

Screening and Diagnostic Tests

FDA-licensed or approved anti-HCV screening tests used in the United States comprise three immunoassays: two enzyme immunoassays (EIA) and one enhanced chemiluminescence immunoassay (CIA).[232,233] Although no true confirmatory test has been developed, supplemental tests for specificity are available. The FDA-licensed or approved supplemental tests include a serological anti-HCV assay, the strip immunoblot assay (Chiron RIBA® HCV 3.0 SIA, Chiron Corp., Emeryville, California), and nucleic acid tests (NAT) for HCV RNA (including reverse transcriptase polymerase chain reaction [RT-PCR] amplification and transcription mediated amplification [TMA]).[234]

Anti-HCV testing includes initial screening with an EIA immunoassay. However, interpretation of the results of EIAs that screen for anti-HCV is limited by several factors: 1) these assays will not detect anti-HCV in approximately 10% of persons infected with HCV; 2) these assays do not distinguish between acute, chronic, or past infection; 3) in the acute phase of hepatitis C, there may be a prolonged interval between onset of illness and seroconversion; and 4) in populations with a low prevalence of infection, the rate of false positivity for anti-HCV is high. If the screening test is positive, either a high screening-test-positive signal-to-cut-off ratio or supplemental testing with a test with high specificity should be performed to verify the results.[232] Among hemodialysis patients, the proportion of false-positive screening test results averages approximately 15%.[232,234] For this reason, one should not rely exclusively on a positive anti-HCV screening-test to determine whether a person has been infected with HCV.

Routine testing of hemodialysis patients for anti-HCV on admission and every 6 months has been recommended since 2001.[232] For routine HCV testing of hemodialysis patients, the anti-HCV screening immunoassay is recommended, and if positive, supplemental anti-HCV testing using RIBA or NAT (Table 23-5). RIBA is recommended rather than NAT because the serological assay can be performed on the same serum or plasma sample collected for the screening anti-HCV screening assay. In addition, in certain situations the HCV RNA results can be negative in persons with active infection. As the titer of anti-HCV increases during acute infection, the titer of HCV RNA declines.[235,236] Thus HCV RNA is not detectable in certain persons during the acute phase of their infection, but this finding can be transient and chronic infection can develop.[236] In addition, intermittent HCV positivity has been observed among patients with chronic HCV infection.[237–239] Therefore the significance of a single negative HCV RNA result is unknown, and the need for further investigation or follow-up is determined by verifying anti-HCV status. There are a number of commercial NAT assays available for the detection (qualitative assays) or quantification (quantitative assays) of HCV RNA available.[233] All currently available assays have excellent specificity, in the range of 98 to 99%. Detection of HCV RNA also requires that serum or plasma

TABLE 23-5 Interpretation of Test Results for Hepatitis C Virus Infection

ANTI-HCV[a] POSITIVE

- An anti-HCV positive result is defined as anti-HCV screening test positive with a high signal-to-cut off ratio; or anti-HCV screening test positive with RIBA positive or NAT positive; or anti-HCV screening test positive, NAT negative, RIBA positive.
- An anti-HCV positive result indicates past or current HCV infection.
- An HCV RNA-positive result indicates current (active) infection, but significance of single HCV RNA negative result is unknown; it does not differentiate intermittent viremia from resolved infection.
- All anti-HCV positive persons should receive counseling and undergo medical evaluation, including additional testing for the presence of virus and liver disease.
- Anti-HCV testing generally does not need to be repeated once a positive anti-HCV result has been confirmed.

ANTI-HCV NEGATIVE

- Anti-HCV negative result is defined as an anti-HCV screening test negative;[b] or anti-HCV screening test positive, RIBA negative; or anti-HCV screening test positive, NAT negative, RIBA negative.
- An anti-HCV negative individual is considered uninfected.
- No further evaluation or follow-up for HCV is required unless recent infection is suspected or other evidence exists to indicate HCV infection (e.g., abnormal liver enzyme levels in immunocompromised persons or persons with other etiology for their liver disease).

ANTI-HCV INDETERMINATE

- An indeterminate anti-HCV result is defined as anti-HCV screening test positive, RIBA indeterminate; or anti-HCV screening test positive, NAT negative, RIBA indeterminate.
- An indeterminate anti-HCV screening test result indicates that the HCV antibody status cannot be determined.
- Can indicate a false-positive anti-HCV screening test result, the most likely interpretation in those at low risk for HCV infection; such persons are HCV RNA negative.
- Can occur as a transient finding in recently infected individuals who are in the process of seroconversion; such individuals usually are HCV RNA positive.
- Can be a persistent finding in an individual chronically infected with HCV; such persons are usually HCV RNA positive.
- If NAT is not performed, another sample should be collected for repeat anti-HCV testing (≥1 month later).

(From the Centers for Disease Control and Prevention, Guidelines for laboratory testing and result reporting antibody to hepatitis C virus, MMWR 52 [RR-3] [2003] 1–15 and www.cdc.gov/hepatitis/HCV/PDFs/hcv_graph.pdf [Cited: June 28, 2010])
[a]Anti-HCV, antibody to hepatitis C virus.
[b]Interpretation of screening immunoassay test results based on criteria provided by the manufacturer.
RIBA, recombinant immunoblot assay; NAT, nucleic acid test.

sample be collected and handled in a manner suitable for NAT and that testing be performed in a laboratory with appropriate facilities established for NAT testing.[232] Although in rare instances, detection of HCV RNA might be the only evidence of HCV infection, a recent study conducted among almost 3000 hemodialysis patients in the United States found that only 0.07% were HCV RNA positive but antibody negative (CDC, unpublished data).

HEPATITIS DELTA VIRUS

Delta hepatitis is caused by the hepatitis delta (HDV), a relatively small defective virus that causes infection in persons with active HBV infection only. The prevalence of HDV infection is low in the United States, with rates <1% among HBsAg-positive persons in the general population and >10% among HBsAg-positive persons with repeated percutaneous exposures (e.g., injecting drug users, persons with hemophilia).[240] Areas of the world with high endemic rates of HDV infection include southern Italy, parts of Africa, and the Amazon basin.[241–243]

Few data exist on the prevalence of HDV infection among chronic hemodialysis patients, and a few studies have reported nonexistent to low prevalence among hemodialysis patients.[244,245] In endemic areas prevalence rates may be relatively high among hemodialysis patients who are HBsAg-positive.[246–248] Only one transmission of HDV has been reported in the United States.[244] In this episode, transmission occurred from a patient who was chronically infected with HBV and HDV to an HBsAg-positive patient after a massive bleeding incident; both patients received dialysis at the same station.

HDV infection may occur as either coinfection with HBV or as a super infection in a person with chronic HBV infection. Coinfections usually resolve, but super infections frequently result in chronic HDV infection and severe disease. High mortality rates are associated with both types of infection. A serological test that measures total antibody to HDV is commercially available.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

During 1985–2002, the percentage of U.S. hemodialysis centers that reported providing chronic hemodialysis for patients with HIV infection increased from 11% to 39%, and the proportion of patients with known HIV infection increased from 0.3% to 1.5%.[70] Although the proportion of patients with HIV infection has remained fairly stable during the past decade, the number of infected patients has increased, as has the number of centers treating patients with HIV infection. HIV is transmitted by blood and other body fluids that contain blood. No patient-to-patient transmission of HIV has been reported in a U.S. hemodialysis center. However, there have been reports of transmission of HIV among patients in other countries. All of these outbreaks have been attributed to several breaks in infection control: 1) reuse of access needles and inadequately disinfected equipment, 2) sharing of syringes among patients, and 3) and sharing of dialyzers among different patients.[249–253] HIV infection is usually diagnosed with assays that measure antibody to HIV, and a repeatedly positive EIA test should be confirmed by Western blot or other confirmatory test.

PREVENTING INFECTIONS AMONG CHRONIC HEMODIALYSIS PATIENTS

Preventing transmission among chronic hemodialysis patients of bloodborne viruses and pathogenic bacteria from both recognized and unrecognized sources of infection requires implementation of a comprehensive infection control program. The components of such a program include infection control practices specifically designed for the hemodialysis setting, such as routine serological testing and immunization, surveillance, and training and education. CDC has published recommendations describing these components in detail.[152]

The infection control practices recommended for hemodialysis units (Table 23-6) will reduce opportunities for patient-to-patient transmission of infectious agents, directly or indirectly through contaminated devices, equipment and supplies, environmental surfaces, or hands of personnel.

TABLE 23-6 Recommended Infection Control Practices for Hemodialysis Units

INFECTION CONTROL PRECAUTIONS FOR ALL PATIENTS

- Wear disposable gloves when caring for the patient or touching the patient's equipment at the dialysis station; remove gloves and perform hand hygiene (if hands are visibly soiled, wash with soap and water) between each patient or station.
- Items taken into the dialysis station should be disposed of, dedicated for use on a single patient only, or cleaned and disinfected before taken to a common clean area or used on another patient.
  - Nondisposable items that cannot be cleaned or disinfected (e.g., adhesive tape, cloth covered blood pressure cuffs) should be dedicated for use on a single patient only.
  - Unused medications (including multidose vials) or supplies (syringes, alcohol swabs, etc.) taken to the patient's station should be used only for that patient and should not be returned to a common clean area or used on other patients.
- When multidose medication vials are used (including vials containing diluents), prepare individual patient doses in a clean (centralized) area away from dialysis stations and deliver separately to each patient. Do not carry multidose medication vials from station to station.
- Do not use common medication carts to deliver medications to patients. Do not carry medication vials, syringes, alcohol swabs, or supplies in pockets. If trays are used to deliver medication to individual patients, they must be cleaned between patients.
- Clean areas should be clearly designated for the preparation, handling, and storage of medications and unused supplies and equipment. Clean areas should be clearly separated from contaminated areas where used supplies and equipment are handled. Do not handle and store medications or clean supplies in the same or adjacent area to where used equipment or blood samples are handled.
- Use external transducer protectors (venous or arterial) for each patient treatment to prevent blood contamination of the dialysis machine's pressure monitoring equipment. Change these external transducer protectors between each patient treatment and when they become wetted,[a] and do not reuse them. The redundant internal transducer protectors do not need to be changed routinely between patients. If the external transducer protectors are contaminated with blood, the internal transducer protector should be checked before dialyzing the next patient.[a]
- Clean and disinfect the dialysis station (chairs, beds, tables, machines, etc.) between patients.
  - Give special attention to cleaning control panels on the dialysis machine and other surfaces that are frequently touched and potentially contaminated with patient's blood.
  - Discard all fluid and clean and disinfect all surfaces and containers associated with the prime waste (including buckets attached to the machines).
- For dialyzers and blood tubing that will be reprocessed, cap dialyzer ports and clamp tubing. Place all used dialyzers and tubing in a leak-proof containers for transport from station to reprocessing or disposal area.

SCHEDULE FOR ROUTINE TESTING FOR HEPATITIS B VIRUS (HBV) AND HEPATITIS C VIRUS (HCV) INFECTIONS

PATIENT STATUS	ON ADMISSION*	MONTHLY	SEMI ANNUAL	ANNUAL
All patients	HBsAg, Anti-HBc (total), Anti-HBs, Anti-HCV, ALT			
HBV susceptible, including vaccine nonresponders		HBsAg		
Anti-HBs positive (≥10 mIU/ml), anti-HBc negative				Anti-HBs
Anti-HBs and Anti-HBc positive		No additional testing is needed		
Anti-HCV negative		ALT	Anti-HCV	

HEPATITIS B VACCINATION

- Vaccinate all susceptible patients against hepatitis B.
- Test for anti-HBs 1–2 months after the last dose.
  - If anti-HBs is <10 mIU/ml, consider patient susceptible, revaccinate with an additional three doses, and retest for anti-HBs.
  - If anti-HBs is >10 mIU/ml, consider immune and retest annually.
- Give booster dose of vaccine if anti-HBs declines to <10 mIU/ml and continue to retest annually.

MANAGEMENT OF HBSAG-POSITIVE PATIENTS

- Follow infection control practices for hemodialysis units for all patients.
- Dialyze HBsAg-positive patients in a separate room using separate machines, equipment, instruments, and supplies.
- Staff members caring for HBsAg-positive patients should not care for HBV susceptible patients at the same time (e.g., during same shift or during patient change over).

[a]FDA Safety Alert (Adapted from CDC, Recommendations for preventing transmission of infections among chronic hemodialysis patients, MMWR Morb Mortal Wkly Rep 50 [RR5] [2001] 1–43).
*Results of HBV testing should be known before patient begins dialysis.
ALT, alanine aminotransferase; Anti-HBc, antibody to hepatitis B core antigen; Anti-HBs, antibody to surface antigen; Anti-HCV, antibody to hepatitis c virus; HBsAg, hepatitis B surface antigen.

These practices should be carried out routinely for all patients in the chronic hemodialysis setting because of the increased potential for blood contamination during hemodialysis and because many patients are colonized or infected with pathogenic bacteria.

Such practices include additional measures to prevent HBV transmission because of the high titer of HBV and its ability to survive on environmental surfaces (see Table 23-6). It is the potential for environmentally mediated transmission of HBV, rather than internal contamination of dialysis machines, that is the focus of infection control strategies for preventing HBV transmission in dialysis centers. For patients at increased risk for transmission of pathogenic bacteria, including antimicrobial-resistant strains, additional precautions also might be necessary in some circumstances. Furthermore, surveillance for infections and other adverse

events is required to monitor the effectiveness of infection control practices, including training and education of both staff members and patients to ensure that appropriate infection control behaviors and techniques are carried out.

In each maintenance hemodialysis unit or facility, policies and practices should be reviewed and updated to ensure that infection control practices recommended for hemodialysis units are implemented and rigorously followed. Intensive efforts must be made to educate new staff members and reeducate existing staff members regarding these practices. Readers should consult the CDC recommendations for details on these practices.[152] The following is a summary of the selected issues.

Routine Testing

All chronic hemodialysis patients should be routinely tested for HBV and HCV infection and the results promptly reviewed to ensure that patients are managed appropriately based on their test results. Test results must be communicated (positive and negative) to other units or hospitals when patients are transferred for care. Routine testing for HDV or HIV infection for purposes of infection control is not recommended in populations with low endemicity (e.g., the United States).

Before admission to the hemodialysis unit, the HBV serological status (i.e., HBsAg, total anti-HBc, and anti-HBs) of all patients should be known. For patients transferred from another unit, test results should be obtained before the patient transfer. If a patient's HBV serological status is not known at the time of admission, testing should be completed within 7 days. The hemodialysis unit should ensure that the laboratory performing the testing for anti-HBs can define a 10 mIU/ml concentration to determine protective levels of antibody.

Routine HCV testing should include use of both a screening immunoassay to test for anti-HCV and supplemental or confirmatory testing with an additional, more specific assay. Use of nucleic acid testing (NAT) for HCV RNA as the primary test for routine screening is not recommended because few HCV infections will be identified in anti-HCV negative patients. However, if ALT levels are persistently abnormal in anti-HCV negative patients in the absence of another etiology, testing for HCV RNA should be considered. Blood samples collected for NAT should not contain heparin, which interferes with the accurate performance of this assay.

Hepatitis B vaccination is an essential component of prevention in the hemodialysis setting. All susceptible patients and staff should receive hepatitis B vaccine. Susceptible patients who have not yet received hepatitis B vaccine, are in the process of being vaccinated, or have not adequately responded to vaccination should continue to be tested regularly for HBsAg. Detailed recommendations for vaccination and follow-up of hemodialysis patients have been published elsewhere.[152]

Management of Infected Patients

Hepatitis B Virus

HBsAg positive patients should undergo hemodialysis in a separate room designated for HBsAg positive patients only. They should use dedicated machines, equipment, and supplies, and most importantly staff members should not care for both HBsAg positive and susceptible patients at the same time (shift) or while the HBsAg positive patient is in the treatment area. Dialyzers should not be reused on HBsAg-positive patients because HBV is efficiently transmitted through occupational exposure to blood and reprocessing dialyzers from HBsAg-positive patients might place HBV-susceptible staff members at increased risk for infection.

HBV chronically infected patients (i.e., those who are HBsAg positive, total anti-HBc positive, and IgM anti-HBc negative) are infectious to others and are at risk for chronic liver disease. They should be counseled on how to prevent transmission to others, especially for those who are their household and sexual partners. Household contacts and sexual partners should be advised to receive hepatitis B vaccine. The HBsAg positive patient should also be evaluated (by consultation or referral, if appropriate) for the presence or development of chronic liver disease according to current medical practice guidelines. It is recommended that individuals with chronic liver disease be vaccinated against the hepatitis A virus (HAV), if susceptible, to prevent any additional injury to the liver.

HBV chronically infected patients do not require any routine follow-up testing for purposes of infection control. However, annual testing for HBsAg is reasonable to detect the small percentage of HBV-infected patients who might lose their HBsAg.

Hepatitis C Virus

HCV-positive patients do not have to be isolated from other patients or dialyzed separately on dedicated machines. The purpose of routine testing is to monitor potential transmission within centers and ensure that appropriate practices are being properly and consistently used. Furthermore, HCV-positive patients can participate in dialyzer reuse programs. Unlike HBV, HCV is not transmitted efficiently through occupational exposures. Thus, reprocessing dialyzers from HCV-positive patients should not place staff members at increased risk for infection.[91,251]

HCV-positive persons should be evaluated (by consultation or referral, if appropriate) for the presence or development of chronic liver disease according to current medical practice guidelines. They also should receive information concerning how they can prevent further harm to their liver and prevent transmitting HCV to others.[254,255] Persons with chronic liver disease should be vaccinated against hepatitis A, if susceptible.

Hepatitis D Virus

Because HDV depends on an HBV-infected host for replication, prevention of HBV infection will prevent HDV infection in a person susceptible to HBV. Patients known to be infected with HDV should be isolated from all other dialysis patients, especially those who are HBsAg positive.

Human Immunodeficiency Virus

Infection control precautions recommended for all hemodialysis patients are sufficient to prevent HIV transmission between patients. HIV-infected patients do not have to be

isolated from other patients or dialyzed separately on dedicated machines. In addition, they can participate in dialyzer reuse programs, because HIV is not transmitted efficiently through occupational exposures. Reprocessing dialyzers from HIV-positive patients should not place staff members at increased risk for infection.

Bacterial/Fungal

Contact transmission can be prevented by hand hygiene,[256] glove use, and disinfection of environmental surfaces. Infection control precautions recommended for all hemodialysis patients are adequate to prevent transmission for most patients infected or colonized with pathogenic bacteria, including antimicrobial-resistant strains. However, additional precautions should be considered for treatment of patients who might be at increased risk for transmitting pathogenic bacteria. Such patients include those with either an infected skin wound with drainage that is not contained by dressings (the drainage does not have to be culture positive for MRSA or VRE or any specific pathogen) or fecal incontinence or diarrhea uncontrolled with personal hygiene measures. For these patients, consider using the following additional precautions:[152]

1. Staff members treating the patient should wear a separate gown over their usual clothing and remove the gown when finished caring for the patient.
2. Dialyze the patient at a station away from the main flow of traffic and with as few adjacent stations as possible (e.g., at the end or corner of the unit).

Vancomycin is used commonly in dialysis patients, in part because vancomycin can be conveniently administered to patients when they come in for hemodialysis treatments. Prudent antimicrobial use is an important component of the CDC recommendations for preventing the spread of vancomycin resistance.[257] Vancomycin is not indicated for therapy (chosen for dosing convenience) of infections because of ß-lactam sensitive gram-positive microorganisms in patients with renal failure.[130,257,258] Depending on the situation, alternative antimicrobials (e.g., cephalosporins) with dosing intervals greater than 48 hours, which would allow post dialytic dosing, could be used. Recent studies suggest that cefazolin given three times a week in the dialysis unit provides adequate blood levels and could be used to treat many infections in hemodialysis patients.[259,260]

Disinfection, Sterilization, and Environmental Cleaning

Good cleaning, disinfection, and sterilization procedures are important components of the infection control program in the hemodialysis center. The procedures do not differ from those recommended for other healthcare settings,[261,262] but the high potential for blood contamination makes the hemodialysis setting unique. Additionally, the need for routine aseptic access of the patient's vascular system makes the hemodialysis unit more akin to a surgical suite than to a standard hospital room. Medical items are categorized as critical (e.g., needles and catheters), which are introduced directly into the bloodstream or normally sterile areas of the body; semicritical (e.g., fiberoptic endoscopes), which come in contact with intact mucous membranes; and noncritical (e.g., blood pressure cuffs), which touch intact skin only.[262,263]

Cleaning and housekeeping in the dialysis center have two goals: to remove soil and waste on a regular basis, thereby preventing the accumulation of potentially infectious material, and to maintain an environment that is conducive to good patient care.[263] Crowding of patients and overtaxing of staff members may increase the likelihood of microbial transmission. Adequate cleaning may be difficult if there are multiple wires, tubes, and hoses in a small area. There should be enough space to move completely around each patient's dialysis station without interfering with the neighboring stations. Where space is limited, elimination of unneeded items; orderly arrangement of required items; and removal of excess lengths of tubes, hoses, and wires from the floor can improve accessibility for cleaning. Because of the special requirements for cleaning in the dialysis center, staff should be specially trained in this task.

After each patient treatment, frequently touched environmental surfaces, including external surfaces of the dialysis machine, should be cleaned (with a detergent) or disinfected (with a detergent germicide). A recent study in the Netherlands where the investigators used luminol to detect nonvisible blood contamination has demonstrated the importance of environmental cleaning.[264] It is the cleaning step that is important for interrupting the cross contamination transmission routes.[265,266] Antiseptics, such as formulations with povidone iodine, hexachlorophene, or chlorhexidine, should not be used, because these are formulated for use on skin and are not designed for use on hard surfaces.

There is no evidence that medical waste is any more infectious than residential waste or has caused disease in the community.[267] Wastes from a hemodialysis center that are actually or potentially contaminated with blood should be considered infectious and handled accordingly. Eventually, these items of solid waste should be disposed of properly in an incinerator or sanitary landfill, depending on state or local laws.

Standard protocols for sterilization and disinfection are adequate for processing any items or devices contaminated with blood. Historically there has been a tendency to use "overkill" strategies for instrument sterilization or disinfection and housekeeping protocols. This is not necessary. The floors in a dialysis center are routinely contaminated with blood, but the protocol for floor cleaning is the same as for floors in other healthcare settings. Usually, this involves the use of a good detergent germicide; the formulation can contain a low or intermediate level disinfectant.

Bloodborne viruses, such as HBV and HIV, are inactivated by any standard sterilization systems such as standard steam autoclave cycles of 121°C (249.8°F) for 15 minutes, ethylene oxide gas,[262] and low temperature hydrogen peroxide gas plasma.[268] Large blood spills should be cleaned to remove visible material; the presence of organic soil can interfere with the activity of the disinfectant. Once the visible soil has been removed the area should receive low to intermediate level disinfection following the label directions of the germicide manufacturer.

Blood and other specimens, such as peritoneal fluid, from all patients should be handled with care. Peritoneal fluid can contain high levels of HBV and should be handled in the same manner as the patient's blood.[269] Consequently, if the

center performs inpatient peritoneal dialysis, the same criteria for separating HBsAg positive patients who are undergoing hemodialysis apply to those undergoing peritoneal dialysis.

HBV has not been grown in tissue cultures, and without a viral assay system, studies on the precise resistance of this virus to various chemical germicides and heat have not been performed. However, the resistance of HBV to heat and chemical germicides may approach that of some other viruses and bacteria but certainly not that of the bacterial endospore or the tubercle bacillus. Further, studies have shown that HBV is not resistant to commonly used high level and intermediate level disinfectants.[270,271]

Blood contamination of venous pressure monitors has been implicated in HBV transmission.[272] Therefore, external pressure transducer filters should be used; these filters should not be reused.

In single pass artificial kidney machines, the internal fluid pathways are not subject to contamination with blood. Although the fluid pathways that exhaust dialysis fluid from the dialyzer may become contaminated with blood in the event of a dialyzer leak, it is unlikely that this blood contamination will reach a subsequent patient. Therefore, disinfection and rinsing procedures should be designed to control contamination with bacterial rather than blood borne pathogens.

For dialysis machines that use a dialysate recirculating system (such as some ultrafiltration control machines and those that regenerate the dialysate), a blood leak in a dialyzer, especially a massive leak, can result in contamination of a number of surfaces that will contact the dialysis fluid of subsequent patients. However, the procedures that are normally practiced after each use of a recirculating machine—draining of the dialysis fluid, subsequent rinsing, and disinfection—will reduce the level of contamination to below infectious levels. In addition, an intact dialyzer membrane will not allow passage of bacteria or viruses. Consequently, if a blood leak does occur with either type of dialysis machine, the standard disinfection procedure used for machines in the dialysis center to control bacterial contamination will also prevent transmission of blood borne pathogens.

FUTURE DIRECTIONS

Infection control strategies that prevent and control HBV infection among hemodialysis patients have been well-established. Areas that need further research include determining the ideal hepatitis B vaccine dosage regimen for predialysis and post dialysis pediatric patients and for predialysis adult patients and the optimal timing for follow-up testing and administration of booster doses among vaccine responders. With regards to HCV infection, further studies are needed to clarify the specific factors responsible for transmission of HCV among hemodialysis patients and to evaluate the effect of the current recommendations on prevention and control of HCV infection in this setting.

Many areas related to the occurrence of bacterial and fungal infections in maintenance hemodialysis patients need additional information. Studies are needed on the prevalence and epidemiology of these infections among chronic hemodialysis patients and the patient care practices (e.g., those related to vascular access care and cannulation) that would be most useful in preventing infections. Because dialysis patients play a prominent role in the epidemic of antimicrobial resistance, more research regarding optimal strategies to ensure judicious use of antimicrobials in these patients should be conducted. Additional research topics would also include determining the frequency of transmission of pathogens within the dialysis unit and whether additional precautions are necessary to prevent such transmission.

A full list of references are available at www.expertconsult.com.

Chapter 24

ACUTE COMPLICATIONS ASSOCIATED WITH HEMODIALYSIS

Orfeas Liangos, M.D., F.A.C.P., F.A.S.N., and Bertrand L. Jaber, M.D., M.S., F.A.S.N.

Since first successfully performed in 1945,[1] hemodialysis (HD) has become a routine procedure. However, despite significant improvements in HD equipment and patient monitoring, acute complications can still occur during the therapy. This chapter will review acute complications that are encountered during or are directly related to HD. The chronic complications of dialysis have been extensively reviewed elsewhere.[2,3]

DIALYSIS REACTIONS

Adverse reactions occurring during HD may be caused by the exposure of patient blood to surface components of the extracorporeal circuit including the dialyzer, tubing, and other compounds used in the manufacturing and sterilization processes. This interaction between the patient's blood and the extracorporeal system can lead to various adverse reactions that can range in severity from mild to life-threatening anaphylactic/anaphylactoid reactions (Table 24-1).[4]

LIFE-THREATENING ANAPHYLACTIC/ANAPHYLACTOID REACTIONS

Anaphylaxis is the result of an immunoglobulin E (IgE)-mediated acute allergic reaction in a sensitized patient, whereas anaphylactoid reactions result from the direct release of mediators by host cells. Symptoms typically develop within the first 5 minutes of dialysis initiation, although they may be delayed by up to 20 minutes. The severity can range from mild to life-threatening and can encompass a burning or heat sensation throughout the body or at the access site; dyspnea; chest pressure or tightness; angioedema/laryngeal edema; acral or oral paresthesia; rhinorrhea; lacrimation; sneezing or coughing; flushing; pruritus; and nausea/vomiting, abdominal cramps,

TABLE 24-1 Development, Management, and Prevention of Dialysis Reactions

DIALYSIS REACTION	ONSET DURING HEMODIALYSIS	ETIOLOGY	COURSE OF ACTION	PREVENTION
Life-threatening anaphylactic/ anaphylactoid reaction	5-20 minutes	- Ethylene oxide (first-use dialyzer syndrome) - Germicide (reuse dialyzer syndrome) - AN69 dialyzer and ACE inhibitor interaction - Renalin dialyzer reuse and ACE inhibitor interaction - Medications (parenteral iron, heparin)	Stop hemodialysis Do not return blood to patient Epinephrine Corticosteroids Antihistamines	Rinse dialyzer before use Use gamma/steam/electron-beam sterilized dialyzer Discontinue dialyzer reuse Avoid AN69 dialyzer with ACE inhibitor Discontinue reuse with renalin Use test dose for parenteral iron
Non-life-threatening reaction	20-40 minutes	Complement activation	Continue hemodialysis	Use noncellulose dialyzer membrane
Pyrogen reaction	Anytime	Endotoxin/bacterial contamination	Stop hemodialysis if hypotension present Blood cultures Antibiotics Antipyretics	Preventive strategies

and diarrhea. A history of atopy, elevated total serum IgE, eosinophilia, and the use of angiotensin converting enzyme (ACE) inhibitors and (but less frequently) angiotensin receptor blockers predispose the patient to such reactions.[5,6] The etiology of dialysis reactions (DR) is diverse and requires prompt investigation to help prevent further reactions.

Leachables

Allergy to Ethylene Oxide: First Use Syndrome

Ethylene oxide (ETO), the dialyzer manufacturer's gas sterilant, can cause DR by acting as a hapten through binding to albumin. Specific IgE antibodies against ETO conjugated to human serum albumin (HSA) have been detected using a radioallergosorbent test (RAST).[7] However, only two-thirds of patients with such reactions have circulating IgE antibodies against ETO-HSA, whereas one third do not. Of note, circulating levels of anti-ETO-HSA IgE antibodies can be detected in up to 10% of patients with no prior history of DR.[8] The potting compound used to anchor the hollow fibers in the dialyzer housing acts as a reservoir for ETO and may impede its washout from the dialyzer. ETO may still be detectable after long periods of thorough rinsing of the dialyzer.[9] Furthermore, delayed entry of ETO into the priming fluid has also been observed, and dialyzer reprocessing before first use has reduced the incidence of these reactions.[4] Testing for ETO-specific IgE antibodies may be helpful if an ETO allergy is suspected.[10] Once the diagnosis has been confirmed or is highly suspected, ETO-sterilized dialyzers should be replaced with gamma-, steam-, or electron-beam-sterilized dialyzers. Of note, a survey suggests that allergic reactions to ETO are declining in frequency.[11]

Dialyzer's Reuse Reactions: Reuse Syndromes

Most residual ETO is washed out of the dialyzer during "*first use*" and with subsequent reprocessing. Thus reuse reactions are more likely due to other agents, such as the germicides used for dialyzer reprocessing. Commonly used germicides include formaldehyde, glutaraldehyde, and peracetic acid/hydrogen peroxide. Formaldehyde is a known allergen, and life-threatening reactions have been observed in HD patients in whom the RAST to formaldehyde was positive.[6,12] Exposure may also result from residual formaldehyde after disinfection of the water supply system.[13]

Other Leachables

Isopropyl myristate used in the solution spinning process of hollow fiber fabrication, isocyanates found in the potting compound, and nonendotoxin LAL-reactive material believed to be cellulose in nature and found during rinsing of cellulose hollow-fiber dialyzers have also been suspected to cause DR.[4]

Membrane Bioincompatibility

Evidence to support the hypothesis that life-threatening reactions follow complement activation during dialysis with unsubstituted cellulose membranes has been disputed.[4] Indeed, although complement activation does occur during dialysis, it does not prove causality because severe anaphylaxis results in complement activation.[14] However, it is possible that secondary or concomitant release of complement fragments may amplify an IgE-mediated ETO reaction, for instance, by enhancing release of histamine or other mediators.[15]

Bradykinin-Mediated Reactions

Polyacrylonitrile (PAN) is a negatively charged synthetic membrane, which is composed of a copolymer of acrylonitrile and an aryl sulfonate.[16] In the 1990s, severe anaphylactoid reactions were reported in patients dialyzed with PAN membranes who were also on ACE inhibitors.[18] Binding of Hageman factor XII to a negatively charged membrane leads

to formation of kallikrein from prekallikrein and the subsequent release of kinins (i.e., bradykinin) from kininogen. Although cuprophane and polymethylmethacrylate (PMMA) membranes display an ability to activate factor XII, PAN activates it to a greater extent.[19] Bradykinin, a molecule with a very short half-life, in turn, activates production of prostaglandin and histamine release, with subsequent vasodilatation and increased vascular permeability.[20] ACE inactivates bradykinin, and therefore, ACE inhibitors can prolong the biological activities of bradykinin, which are highly calcium-dependent.[4]

Several anaphylactoid reactions have also been reported in patients dialyzed with bleach reprocessed polysulfone (PS) membranes and treated with ACE inhibitors.[21] These reactions ceased once the use of bleach was discontinued. Furthermore, a cluster of anaphylactoid reactions was observed in patients dialyzed with different membranes who were also taking ACE inhibitors.[22] Hydrogen peroxide/peracetic acid was the reprocessing agent used, and the reactions abated once reprocessing was discontinued, despite continued use of ACE inhibitors.[23]

Dialysate Factors

The use of acetate dialysate has been implicated in DR, and proposed mechanisms include interleukin 1 (IL-1) production by monocytes and prostaglandin/adenosine-mediated mechanisms.[4] Conversely, bicarbonate dialysate is highly susceptible to bacterial contamination, and bacterial products present in the dialysate can diffuse across both high-flux and low-flux membranes (see Bacterial Contamination).[24,25] Further, reprocessing of dialyzers, particularly with bleach, can increase the likelihood of reverse transfer of bacterial products from the dialysate to blood.[24] These bacterial products can induce cytokine release by monocytes and consequently pyrogen reactions (PRs). Although PRs during dialysis are reported with a high frequency in dialysis units that use high-flux or reprocessed dialyzers,[26] some authors suggest that they do not cause life-threatening reactions.[27]

Drug-Induced Reactions

Intravenous Iron

Dextran, a mixture of synthetic glucose polymers has been associated with systemic reactions.[28] Anaphylactic reactions to iron dextran are due to this compound and occur in 0.6%–1% of recipients.[4] The National Kidney Foundation's Clinical Practice Guidelines recommend availability of resuscitation equipment and personnel whenever iron dextran is administered.[29] Differences in the frequency of anaphylactic reactions between high and low molecular weight iron dextran preparations have been reported, and the latter preparations appear to be safer.[30] The precise mechanisms responsible for dextran-induced anaphylactoid reactions are elusive, but there seems to be dose-dependent basophil histamine release that may account for the cardiovascular collapse.[4] Because this dose-related toxicity, iron dextran should always be initiated as a 0.5- to 1-mg test dose, with staff available to respond to reactions. If the test dose is uneventful, a course of therapy can then be given safely (i.e., 100-200 mg per dialysis session for 10 doses).[31] Intravenous iron gluconate and saccharate are therapeutic alternatives to iron dextran and confer less anaphylactic reactions, but inflammatory reactions related to free iron release following injection of these drugs have been recognized.[32] Ferumoxytol, a polyglucose sorbitol carboxymethylester-coated iron oxide nanoparticle that was recently approved by the U.S. Food and Drug Administration (FDA), allows for a safer administration of larger bolus doses of intravenous iron,[33] but its long-term safety in clinical practice remains to be determined.

Heparin

Patients rarely exhibit hypersensitivity to heparin formulations, but usually respond by substituting beef with pork heparin, or vice versa.[4] Heparin reduces aldosterone secretion by a direct action on the adrenal gland, leading to hyperkalemia. It is not clear, however, whether this effect is due to heparin or its preservative chlorbutol.[34] The resultant hyperkalemia may be clinically significant in patients with underlying chronic kidney disease.[35] However, this phenomenon has not been studied in the dialysis population, and heparin-associated complications are mainly related to bleeding (see Hemorrhage) or thrombocytopenia (see Hematological Complications). Several deaths from anaphylactoid reactions in dialysis patients were recently reported and ultimately linked to heparin products originating from one plant in China, which were contaminated with oversulfated chondroitin sulfate.[36]

Desferrioxamine

Desferrioxamine therapy for aluminum or iron chelation can produce hypotension during dialysis or rare, allergic reactions, gastrointestinal disturbances, loss of vision, auditory toxicity, bone pain, or exacerbation of aluminum encephalopathy.[37]

Treatment and Prevention

The treatment of a severe anaphylactic/anaphylactoid reaction is similar and requires immediate cessation of HD without returning the extracorporeal blood to the patient's circulation. Antihistamines (H_1- and H_2-antagonists), epinephrine, corticosteroids, and respiratory support should be provided, if needed.[38] Specific preventive measures include rinsing the dialyzer immediately before first use, substituting ETO- with gamma-, electron beam or steam-sterilized dialyzers and avoiding PAN membranes in patients on ACE inhibitors.

MILD REACTIONS

Mild reactions consisting of chest/back pain often occur 20–40 minutes after initiation of HD. They are not characterized by anaphylactic or allergic reactions, and dialysis can usually be continued. Symptoms usually abate after the first hour, suggesting a relation to the degree of complement activation.[39] Indeed, these reactions decrease with the use of substituted and reprocessed unsubstituted cellulose membranes, particularly when bleach has been omitted from the

reuse procedure.[4] Some studies suggest that the incidence of chest/back pain parallels the degree of complement activation and increases with larger surface-area dialyzers.[4] However, a randomized crossover study comparing two similar size unsubstituted cellulose and PAN dialyzers showed no difference in these reactions between the two membranes, in spite of differences in complement activation.[40] Treatment with oxygen and analgesics is usually sufficient, and preventive measures include automated cleansing of new dialyzers or using noncellulose membranes.

MICROBIAL CONTAMINATION

Naturally occurring water bacteria commonly found in HD water systems include gram-negative bacteria (GNB) such as *Pseudomonas* species and nontuberculous mycobacteria. GNB release endotoxin or lipopolysaccharide (LPS), and other bacterial products, and nontuberculous mycobacteria are highly resistant to germicides.[4] Several factors that are operative during dialysis place patients at risk for exposure to bacteria and/or bacterial products, including contaminated water or bicarbonate dialysate, improperly sterilized dialyzers, and cannulation of infected grafts or fistulas.

Bicarbonate-containing solutions are highly susceptible to bacterial contamination.[4] If stored for too long, sodium bicarbonate breaks down to sodium carbonate, which, along with glucose contained in the dialysate, constitutes a growth medium for bacteria. When GNB reach excessively high concentrations in the dialysate, serious health risks to patients, including PRs with or without bacteremia, can result.[41] Indeed, outbreaks of clusters of infection in HD patients have been ascribed to bacterial contamination (Table 24-2). The passage of endotoxin from the dialysate into the blood can occur by diffusion or convection. The use of high-flux dialyzers, especially those reprocessed with bleach (which increases the permeability), increases the risk of passage of endotoxin, particularly lipid A (~2000 Da), the active moiety of LPS, from dialysate into blood. LPS interacts with plasma LPS Binding Protein (LBP) and mediates cytokine production by interacting with the monocyte CD14 receptor.[42] The subsequent release of pyrogenic cytokines such as interleukin-1 (IL-1) and tumor necrosis factor produce a transient febrile reaction.

Reprocessing of dialyzers has become a common practice in the United States because of decreased cost, improved biocompatibility, and fewer patient symptoms.[4] However, despite general safety of the procedure, PRs and bacteremia may supervene. Reprocessing involves rinsing, cleaning, testing, and sterilizing hollow fiber dialyzers. PRs as a result of reprocessing have been attributed to improper disinfection procedures, inadequate potency of the solution used to disinfect the dialyzer, and inadequate measures to disinfect the O-rings of dialyzers with removable headers.[4] In a survey by the Centers for Disease Control (CDC) and Prevention in the United States, the incidence of PR in the absence of septicemia were reported by 19% of U.S. dialysis centers.[26] Furthermore, the use of high-flux dialyzers (especially in conjunction with bicarbonate dialysate) and reprocessed dialyzers was associated with an increased incidence of PR.[26] Finally, intradialytic hypotension can also cause transient mesenteric ischemia that may be sufficient enough to damage the gastrointestinal mucosa and lead to bacterial and/or LPS translocation.[42]

Pyrogenic reactions should be entertained after septicemia has been ruled out. Careful examination of the dialysis access is warranted and blood cultures should be obtained. Treatment of PR includes antipyretics, empiric broad-spectrum antibiotics, discontinuation of ultrafiltration whenever hypotension is present, and selective hospitalization. An outbreak of bacteremia among several patients, involving a similar organism should prompt thorough search for bacterial contaminants of the dialysis equipment.

TABLE 24-2 Pyrogenic Reactions/Infections Related to Microbial Contamination of Dialysis Fluids

CAUSATIVE AGENTS	IDENTIFIABLE SOURCES OF CONTAMINATION	MANIFESTATIONS
Bacterial Products		
- Lipopolysaccharide - *Microcystis aeruginosa* exotoxin (Microcystin-LR)	- Backfiltration from bicarbonate/glucose dialysate - High-flux dialysis - Highly reprocessed dialyzers - Gut translocation following intradialytic hypotension - Carbon filters contaminated by blue green algae	- PR without bacteremia - Acute hepatic necrosis
Bacteria		
- *Klebsiella pneumoniae* - *Pseudomonas* species - *Xanthomonas maltophilia* - *Citrobacter freundii* - *Acinetobacter* species - *Enterobacter* species - *Bacillus* species - *Achromobacter*	- O-rings - Hose connected to water spray device - Cross-contamination by technician's gloves - Cross-contamination of blood tubing by ultrafiltrate waste bag - Low levels of disinfectant - Inadequate mixing of disinfectant with tap water - Inadequate potency of disinfectant despite standard measures	- PR with bacteremia
Mycobacteria		
- Mycobacterium chelonae abscessus	- Inadequate potency of disinfectant despite standard measures	- PR with mycobacteremia - Soft tissue infection - Arteriovenous graft infection
Yeast		
- Rhodotorula glutinis	- Drain of hemodialysis machines	- Unknown

PR, pyrogen reaction.

TABLE 24-3 Strategies for Prevention of Bacterial Contamination

STRICT ADHERENCE TO AAMI STANDARDS FOR FLUID QUALITY	TYPE OF FLUID	TOTAL VIABLE MICROBIAL COUNT	ENDOTOXIN LEVEL
	Product water (to prepare dialysate or concentrates from powder, or to process dialyzers)†	<200 CFU/ml	<2 EU/ml
	Conventional dialysate†	<200 CFU/ml	<2 EU/ml
	Ultrapure dialysate	<0.1 CFU/ml	<0.03 EU/ml
Appropriate Germicide	- 4% formaldehyde* - 1% formaldehyde heated to 40°C*‡ - Glutaraldehyde‡ - Hydrogen peroxide/peracetic acid mixture (Renalin)*‡ - Heat sterilization (105°C for 20 hours) for reprocessing of polysulfone membranes‡		
Wash and rinse the vascular access arm with soap and water.			
Before cannulation, inspect vascular access for local signs of inflammation.			
Scrub the skin with povidone iodine or chlorhexidine; allow to dry out for 5 minutes before cannulation.			
Record temperature before and at the end of dialysis.			
When central delivery systems are used:	- Clean and disinfect connecting pipes regularly. - Remove residual bacteria or endotoxin by additional filtration.		
When single-patient proportioning dialysis machines are used:	- Freshly prepare bicarbonate dialysate on a daily basis. - Discard unused solutions at the end of each day. - Containers should be rinsed and disinfected with fluids that meet AAMI standards and air-dried before dialysate preparation.		

AAMI, Association for the Advancement of Medical Instrumentation; *CFU,* colony-forming unit.
*A minimum of 11- or 24-hour exposure to peracetic acid or formaldehyde is required, respectively.
‡These germicides are all equivalent or superior to 4% formaldehyde.
†The action level for the total viable microbial count in the product water and conventional dialysate is 50 CFU/ml, and the action level for the endotoxin concentration is 1 EU/ml.

Strategies for the prevention of PRs are summarized in Table 24-3 and start with strict adherence to the Association for the Advancement of Medical Instrumentation (AAMI) standards (Dialysate for Hemodialysis. In American National Standards, Association for the Advancement of Medical Instrumentation, Arlington, 2009, 1–66). In an era of high-flux dialysis and reuse, some authors believe that these recommendations are too liberal and that sterile-pyrogen-free dialysis fluids be used.[43] Although this approach may offer clear advantages to patients, skepticism with regards to cost remains an unresolved issue and data to support its benefit are currently lacking.

INVESTIGATION OF A DIALYSIS OUTBREAK

The CDC define the term "*outbreak*" as "the occurrence of more cases of disease, injury, or other health condition than expected in a given area or among a specific group of persons during a specific period."[44] A common cause of the disease or a relationship between the cases is usually presumed.[44,45] In the dialysis unit environment, both infectious and noninfectious causes can lead to an outbreak. Infectious causes can be blood-borne, airborne, waterborne,[46] or transmitted through direct contact by the dialysis unit staff. Noninfectious causes can be related to dialysis water contamination,[47] errors in dialysate composition or contaminants in medications or devices applied during dialysis. The investigation of a dialysis outbreak requires a systematic approach and a critical review the medical records and all the steps of the dialysis procedure. Although the etiology is usually easily identified, more esoteric causes of dialysis outbreaks that may have to be considered include water contamination with bacterial toxins,[48] medication impurities,[36] bacterial contaminants,[49] systemic embolization of degraded dialyzer membrane polymer as a result of prolonged or improper storage,[50] and hemolysis as a result of faulty blood-line tubing sets.[51]

BLOOD-LINE TOXICITY

Particle Spallation

Blood-line components may enter the circulation by spallation, which is the release of silicone (not used in the United States) or polyvinyl chloride (PVC) particles, induced by the roller pump.[52,53] Studies of the bioengineering aspects of spallation indicate that the origin of these particles is from cracks in the pump insert material near the point of flexing caused by the repeated compression/relaxation of the tubing by the rollers.[53] With current high-flux technology demanding high pump speed performances, spallation is more likely to occur. Quantitative studies indicate that the majority of particles released are <5μm in diameter and that the greatest release of particles occurs during the first hour of pumping.[54] Even though PVC has largely replaced silicone, the problem of spallation persists.[54] Loading of animals with PVC or silicone particles induces IL-1 and prostanoid secretion by macrophages,[55,56] and ascribed clinical and pathological effects in humans include hepatomegaly, granulomatous hepatitis and hypersplenism.[53] Silicon-related toxicity with plasma levels greater than 2 mg/L has been described in two dialysis patients.[57] Although it was not related to dialysis-related contamination, the syndrome was characterized

by perforating folliculitis and aberrant hair growth.[57] Future bioengineering advances aimed at improving blood-line biocompatibility are warranted, including newer design of roller and pump segments and internal coating of PVC tubing.

Leachables

The flexibility of PVC is achieved by the addition of a plasticizer, di(2-ethylhexyl) phthalates (DEHP).[58] Phthalates are physically linked but not bound to PVC and hence may leach from the tubing matrix into the circulation. DEHP has been recovered from plasma and erythrocytes that were stored in plastic tubes.[53] Although there is no clear evidence to confirm its toxicity, DEHP can bind to plasma lipids and lipoproteins and significant tissue levels have been recovered at autopsy.[53] Furthermore, a hepatitis like syndrome and necrotizing dermatitis have been reported in association with PVC exposure.[53] In the dermatological literature, contact dermatitis due to DEHP exposure has been described.[59]

Leachability studies of a newer plasticizer, trimellitate from blood tubing demonstrate a lower release when compared to DEHP.[60] Of note, the AAMI standards do not enforce leachability and spallation study requirements from manufacturers of blood-line tubing and dialysis equipment.

CARDIOVASCULAR COMPLICATIONS

Intradialytic Hypotension

Intradialytic hypotension requiring medical intervention occurs in 10%–30% of treatments.[61] Although it may be frequently asymptomatic, it can also be accompanied by a severe compromise of vital organ perfusion resulting in loss of consciousness, seizures, and even death. Associated vomiting may be complicated by aspiration.

The pathogenesis of intradialytic hypotension is multifactorial. Ultrafiltration rate, total volume of fluid removed, and a reduced plasma-refilling rate coupled with impaired compensatory physiological responses to hypovolemia play a major role. An altered nitric oxide versus endothelin balance has recently been implied in the pathogenesis of intradialytic hypotension.[62] While an ultrafiltration rate of >0.35 ml/kg/min will produce hypotension in most patients,[63] slower ultrafiltration rates with up to a 20% decrease in plasma volume are generally well-tolerated.[64] The failures of normal compensatory responses to hypovolemia, which include central redistribution of the blood volume and increase in peripheral vascular resistance, are frequent mechanisms in hypotensive episodes. Patient-related factors include autonomic dysfunction (i.e., baroreflex impairment and alteration of heart rate responses) particularly in elderly and diabetic patients, use of antihypertensive medications, structural heart disease, cardiac arrhythmias, bacterial sepsis, hemorrhage, intradialytic venous pooling, increase in core body temperature, ingestion of food during dialysis, and anemia. Dialysis associated L-carnitine deficiency may also contribute to intradialytic hypotension.[65] In addition, "*sympathetic failure*" may be a manifestation of baroreflex dysfunction due to a lack of appropriate rise in plasma norepinephrine levels during HD.[66] The decreased sensitivity of the renin-angiotensin, adrenergic and arginine vasopressin systems could also contribute to inadequate vasoactive responses to HD-induced hypovolemia.[67]

Immediate management of intradialytic hypotension consists of restoration of vital organ perfusion by placing the patient in a Trendelenburg position while preventing aspiration, augmentation of the circulating blood volume through infusion of isotonic normal saline, hypertonic agents, and reduction/cessation of ultrafiltration.

Cardiovascular instability and intradialytic hypotension can also be reduced with the use of bicarbonate dialysate, volumetric control of ultrafiltration, increased dialysate sodium concentration, better assessment of patient's "*dry weight*" using bioelectric impedance or vena caval ultrasound, and the use of cooler temperature dialysis.[68] Sodium modeling also reduces hypotensive episodes.[69] The use of salt poor albumin offers no advantage to normal saline but costs more. On-line blood volume monitoring techniques have been used to control intradialytic hypotensive episodes, but their effectiveness is controversial.[70,71] Other preventive strategies include correction of anemia and hypoalbuminemia, withdrawal of antihypertensive drugs before dialysis, avoiding food before and during dialysis, counseling patients regarding weight gain, treatment of congestive heart failure and arrhythmias, and search for other causes such as pericardial effusion. Finally, the predialysis use of midodrine, a selective alpha-1-adrenergic receptor agonist, is effective and safe in reducing the severity and frequency of hypotensive episodes.[72] Other pharmacological options include the use of L-carnitine and setraline.[73,74]

Intradialytic Hypertension

Intradialytic hypertension occurs in 8% to 30% of treatments,[75] and might be a risk factor for cardiovascular morbidity and mortality. In one study, an increase in arterial blood pressure during dialysis was associated with an increased risk of hospitalization or death at 6 months when compared to a decrease in blood pressure during dialysis.[76] Time-averaged blood pressure measurements correlate better with postdialysis than with predialysis blood pressure, and dialysis patients often fail to show the normal "*nocturnal dip*" in blood pressure.[77,78] Elevated postdialysis pulse pressure was associated with a 12% increase in the hazard for death, whereas postdialysis systolic blood pressure was inversely related to mortality.[79]

Although volume control is still the mainstay of blood pressure management in dialysis patients, blood pressure control is not achieved despite fluid removal in up to 50% of patients.[80] Preexisting hypertension, volume depletion, hypokalemia-induced increased renin-angiotensin secretion,[81] hypercalcemia-induced increased inotropism, and vascular tone[82] have all been associated with volume-independent hypertension in HD.[83] Other hypothesized mechanisms of intradialytic hypertension include increase in sympathetic tone[84] and increased cardiac output in response to fluid removal, particularly among patients with cardiac dysfunction.[85] The chronic administration of recombinant human erythropoietin (rHuEPO) has also been associated with hypertension. This effect may be mediated by rheological mechanisms and humoral factors such as elevation in resting

and agonist-stimulated cytoplasmic calcium concentration, increased endothelin production, upregulation of tissue renin and angiotensinogen expression, and a possible change in vascular tissue prostaglandin production.[86]

If signs or symptoms of volume contraction are lacking, it is justified to reduce the dry weight by 0.5 kg, observe the clinical response, and reevaluate periodically. Increases in dialysis or ultrafiltration time and/or frequency may facilitate volume removal. Atrial natriuretic peptide measurements indicate that a substantial fraction of patients with dialysis-refractory hypertension are not at their *"true dry weight."*[87] Changing the administration of rHuEPO from the intravenous to the subcutaneous route has been associated with improved blood pressure control in hypertensive dialysis patients.[88] Finally, consideration should be given to the use of minimally or nondialyzable antihypertensive medications such as angiotensin receptor blockers, calcium channel blockers, clonidine, and carvedilol.

Cardiac Arrhythmias

Intradialytic atrial and ventricular arrhythmias are common in HD patients and the etiology is often multifactorial. Frequently encountered underlying conditions include ischemic or hypertensive heart disease, left ventricular hypertrophy and or dysfunction, uremic pericarditis, silent myocardial ischemia, and conduction system calcification.[89–92] In addition, acute and chronic alterations in fluid, electrolyte, and acid/base homeostasis may enhance the arrhythmogenic properties of digitalis preparations, antiarrhythmic and other drugs,[90] or simply increase myocardial oxygen delivery or consumption such as in intradialytic hypotension or volume overload, respectively.

Measures to prevent arrhythmias include the use of bicarbonate dialysate and careful attention to dialysate potassium and calcium levels. Use of zero potassium dialysate should be discouraged because of arrhythmogenic potential, and potassium modeling may be useful.[93] In patients on digitalis, intracellular potassium shifts during dialysis should be minimized. Serum digoxin levels should be regularly monitored and the need for the drug regularly reassessed. Dialysate calcium levels of 3.5 mEq/L have been associated with cardiac ectopy,[94] and the use of the recommended dialysate calcium level of 2.5 mEq/L has also been associated with a prolonged QT interval and increased QT dispersion.[95] QT dispersion, a measure of the variation in QT interval length on a standard 12-lead electrocardiogram, appears to reflect on the inhomogeneity in ventricle repolarization and has been used to predict the risk of malignant cardiac arrhythmia. In HD patients, QT dispersion correlates with left ventricular hypertrophy and mass and has been shown to improve following kidney transplantation.[96,97]

Similar to the general population, HD patients who develop atrial fibrillation have an increased risk of thromboembolic complications and may benefit from anticoagulation.[98]

Sudden Death

Based on data from the United States Renal Data System, 42% of dialysis patient deaths were documented as sudden or cardiac in origin, with 22% of deaths related to cardiac arrests and arrhythmia.[99] Excess mortality (approximately 20% of all deaths occurring per week) was noted on Mondays for patients dialyzing on Mondays, Wednesdays, and Fridays, and on Tuesdays for those dialyzing on Tuesdays, Thursdays, and Saturdays. No excess mortality on a particular day of the week was found in patients on peritoneal dialysis. These observational studies suggest that the cause of death may be the result of the discontinuous nature of HD.[99] Elevations of cardiac troponin T[100] and elevations of serum phosphate and calcium phosphate product[101] have also been associated with an increased risk of death in dialysis patients.

Patients who sustain a cardiac arrest in the dialysis facility tend to be older and are more likely to have diabetes mellitus and a dialysis catheter for vascular access. They also tend to have had a recent hospitalization and often experience a blood pressure drop before the cardiac arrest.[102] There has been particular interest in the occurrence of ventricular ectopic activity in HD patients and risk factors such as age, left ventricular hypertrophy or dysfunction, and electrolyte disturbances have been entertained. A clear relationship to cardiovascular outcomes however has not been shown to date.

Considering that a variety of psychotropic drugs have been linked to reports of iatrogenic prolongation of the QT interval, cardiac arrhythmia, and sudden death in the general population,[103] a thorough drug history is warranted when investigating sudden cardiac arrest. This is critically important because numerous psychotropic drugs that enter the market may not undergo thorough postmarketing pharmacokinetic studies in dialysis patients.

In the acute management of intradialytic cardiac arrest, other catastrophic intradialytic events need to be ruled out. The prompt recognition and treatment of life-threatening hyperkalemia, and the identification and correction of technical errors such as air embolism, unsafe dialysate composition, overheated dialysate, line disconnection, or sterilant in the dialyzer have to be sought and ruled out. Air in the dialysate, grossly hemolyzed blood, and hemorrhage as a result of line disconnection may be immediately detected. However, if no obvious cause is identifiable, blood should not be returned to the patient, particularly if the arrest occurred immediately upon initiation of dialysis. Complaints of burning at the access site before arrest might indicate an exposure to formaldehyde. If the event occurred during dialysis and a problem with dialysate composition is unlikely, blood may be returned to the patient, blood and dialysate samples should be immediately sent for electrolyte analysis, the dialyzer and blood lines be saved for later analysis, and the dialysis machine replaced until all of its safety features have been thoroughly evaluated for possible malfunction, which will be discussed later. The management of cardiopulmonary arrest during dialysis should follow the guidelines for cardiopulmonary resuscitation.

The potential role of implantable cardioverter defibrillators (ICD) for the primary prevention of sudden death in HD patients with cardiomyopathy has not been investigated to date, but current clinical practice guidelines in general cardiology state that among patients with a left ventricular ejection fraction $\leq$35%, a life expectancy of greater than 1 year, and the fulfillment of other implant criteria, ICD implantation should be considered.[104]

Dialysis-Associated Steal Syndrome

While the construction of an arteriovenous fistula or graft for HD access frequently results in the reduction of blood flow to the hand,[105] clinically significant or symptomatic ischemia, is much more infrequent. Once it becomes symptomatic, however, it can lead to critical limb ischemia and amputation, particularly in patients with peripheral vascular disease and/or diabetes mellitus.[106–108] Fistulas or grafts are classified as small if their diameter is <75% of the diameter of the feeding artery and large if they are >75%. Blood flow in the artery located distal to a small fistula/graft remains orthodirectional, whereas larger fistulas/grafts cause retrograde flow in the distal artery, thus leading to a steal syndrome.[109] Dialysis-associated steal syndrome (DASS) has been reported in 1% and 6% of patients with radiocephalic fistulas and grafts, respectively.[110] Symptoms of numbness, pain and weakness of the hand may appear or worsen during HD, and clinical findings include coolness of the distal arm, diminished pulses, acrocyanosis, and rarely, gangrene. Symptomatic DASS should be differentiated from other causes of painful limbs including dialysis-associated muscle cramps, coexistent polyneuropathy, and entrapment mononeuropathies such as the carpal tunnel syndrome associated with dialysis-related amyloidosis. The syndrome of acute ischemic monomelic mononeuropathy following the creation of an arm access has been described,[107] and rapidly progressing acral gangrene may also be caused by calciphylaxis.[111]

The evaluation of a painful hand includes pulse oxymetry,[112] plethysmography,[110] Doppler flows, and arteriography.[107] The treatment of DASS depends on its clinical severity and the anatomy of the access. The simplest and most effective treatment is ligation of the venous outflow of the fistula/graft.[113] However, this procedure results in the elimination of a site for vascular access and the immediate need to construct another one. Ipsilateral distal revascularization-interval ligation[106] is an alternative surgical technique that preserves vascular access patency and relieves clinical steal symptoms in about 90% of patients.[114] Narrowing or *"banding"* of the fistula/graft to reduce flow[115] can also be used. Intraoperative digital plethysmography,[110] or duplex sonography,[116] may be useful for an early diagnosis or for intraoperative guidance in the correction of DASS. Percutaneous luminal angioplasty or laser recanalization is reserved for patients with inflow or outflow arterial disease.[107,117]

A different DASS that may be of clinical significance was recently reported in dialysis patients with an arteriovenous fistula who received myocardial revascularization with an ipsilateral mammary artery bypass graft. These patients developed a significant reduction in coronary bypass blood flows and myocardial perfusion that was manifest during dialysis.[118]

NEUROLOGICAL COMPLICATIONS

Muscle Cramps

Prolonged involuntary muscle contractions or cramps that occur late in HD and typically involve the legs are the most common acute neuromuscular complications observed during dialysis. They occur in 5%–20% of treatments[119] and frequently lead to premature discontinuation of dialysis. Electromyography performed during HD demonstrates tonic muscle electrical activity, steadily increasing throughout dialysis in those who develop cramps, as opposed to a steady decline in those who do not.[120] Furthermore, some patients have elevated predialysis serum creatine phosphokinase levels during periods of cramps.[121]

The pathogenesis of intradialytic cramps is unknown. Plasma volume contraction and progressive hypoosmolality induced by HD are the two most important predisposing factors.[122] Hypomagnesemia, L-carnitine, and vitamin C and E deficiency have also been incriminated.

The acute management of cramps is directed at increasing the plasma osmolality. Parenteral infusion of 23.5% hypertonic saline (15–20 ml), 25% mannitol (50–100 ml), or 50% dextrose in water (25–50 ml) has been shown to be equally effective.[123] Dextrose in water is preferred because compared to the other agents, it does not cause flushing during infusion nor lead to increased thirst, interdialytic fluid intake, and therefore fluid overload, but it may cause transient hyperglycemia. The use of midodrine may reduce cramps in patients with concomitant symptomatic intradialytic hypotension.[124]

Preventive measures include dietary counseling to reduce excessive interdialytic weight gains. In patients without clinical signs of fluid overload, it is reasonable to increase the dry weight by 0.5 kg and observe the clinical response. In those patients who do not respond to the previously mentioned measures, 5 mg of enalapril twice weekly has been shown to be effective, presumably by inhibiting angiotensin II-mediated thirst.[125] Oral quinine sulfate (325 mg) at the initiation of HD has been shown to significantly reduce the incidence of muscle cramps.[126] However, quinine sulfate is currently not approved as an over-the-counter product for the prevention of cramps and is available by prescription only.[127] The association of quinine with the hemolytic uremic syndrome and the lack of the U.S. Food and Drug Administration's approval, however, should discourage its use. The use of sodium gradient HD is effective in minimizing intradialytic hypoosmolality and preventing hypotension. Different sodium modeling strategies, such as starting from a dialysate sodium concentration of 145–155 mEq/L and decreasing linearly to 135–140 mEq/L[122,128] exponentially or stepwise, have yielded similar clinical results.[129] The use of an intradialytic blood volume ultrafiltration feedback control system has been associated with a lower incidence of cramps.[130] Finally, stretching exercises during dialysis, targeting the affected muscle groups may be beneficial.[128] L-carnitine[65,131] and creatine monohydrate[132] may be effective in decreasing the frequency of muscle cramps. However no large-scale trials have been conducted to prove their efficacy.

Headache

Both historical and contemporary data indicate that dialysis-associated headache is common and occurs in about 60%–70% of patients.[133,134] The symptoms may resemble migraines, tension headaches, or a combination of both.

The etiology of dialysis headache is unknown. It may be a subtle manifestation of the dialysis disequilibrium syndrome (DDS) and in the past may have been related to the use of acetate dialysate. The incidence of headaches seems to be lower with reused than with new dialyzers, with longer than with shorter conventional dialysis treatments, with dialysate containing glucose than with a glucose-free dialysate, and in patients undergoing short daily HD.[135] Furthermore, headaches may be a manifestation of caffeine withdrawal, caused by an acute intradialytic drop in blood caffeine levels in heavy coffee drinkers.[128]

The treatment of dialysis headache consists of oral analgesics (acetaminophen). Preventive measures include a reduction in the blood flow rate during the early part of dialysis. Coffee ingestion during dialysis may also be beneficial.

Restless Legs Syndrome

With a 20%–40% prevalence rate in patients with end-stage renal disease, the restless legs syndrome (RLS) is much more common than in the general population (5%).[136] It has been associated with premature discontinuation of dialysis ("sign-offs").[137] RLS is characterized by deep paresthesia, drawing and crawling sensations in the calves and legs occasionally bordering on pain at the same site, which occur exclusively during rest and inactive seated, or recumbent wakefulness.[138] Movement of the legs yields prompt relief of the symptoms, thus RLS may be responsible for premature discontinuation of a dialysis treatment. Insomnia, anxiety, and mild depression are frequent accompanying symptoms, whereas neurological and electromyographic testing is generally unremarkable. RLS has to be differentiated from peripheral neuropathy in which paresthesia is constant and not relieved by activity. The exact cause of RLS is unknown, but uremic toxins have been implied in its etiology. RLS and insomnia are frequently encountered in severely uremic patients and are relieved within a few weeks of initiating dialysis therapy.[138] RLS symptoms also improve after kidney transplantation.[139] Iron deficiency anemia, vascular insufficiency, chronic lung disease, and caffeine abuse have all been implicated in the pathogenesis of this syndrome.[138]

Short acting benzodiazepines, opiates, and carbamazepine have all been reported to be effective therapies but have the potential for tolerance and abuse. A randomized controlled trial reported on the effectiveness of gabapentin 200–300 mg given after dialysis.[140] Levodopa/carbidopa has also been used with some success.[136] A nonpharmacological approach with transcutaneous electric nerve stimulation is reserved for refractory cases, but experience is limited.[138] In a non-dialysis population, pramipexole, a dopamine receptor agonist, has also been associated with favorable responses.[141] Finally, ropinirole, a dopamine receptor agonist, has shown promising results in dialysis patients.[142]

Dialysis Disequilibrium Syndrome

DSS Still represents a clinical problem in patients with acute and chronic renal failure initiating HD, particularly when the treatment is initiated on a high-flux dialyzer with a large surface area and short dialysis duration. Risk factors include young age, severe azotemia, low dialysate sodium concentration, and preexisting neurological disorders, such as recent stroke, head trauma, subdural hematoma, or malignant hypertension.[143] Use of dialysis machines with volumetric control, bicarbonate dialysate, sodium modeling, and earlier initiation of renal replacement therapy has reduced the incidence of DDS.

Minor symptoms include restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, disorientation, tremor, and hypertension, but major symptoms including obtundation, seizures, coma, cardiac arrhythmias, or death may occur. DDS usually occurs towards the end of dialysis and may be delayed by up to 24 hours. This syndrome is usually self-limited but full recovery may take several days. DDS is a clinical diagnosis, and electroencephalography (EEG) is usually nonspecific, whereas cerebral edema is a consistent finding on computed tomography scan (CT scan). The differential diagnosis includes intracranial hemorrhage, ischemic or hemorrhagic stroke, and Wernicke encephalopathy.[144]

The pathogenesis of DDS, although not fully understood, is largely thought to be the result of cerebral edema.[2] The classic hypothesis includes the development of a transient osmotic disequilibrium as the result of more rapid removal of urea from blood than from cerebrospinal fluid (CSF), leading to an osmotic disequilibrium and subsequent cerebral edema. An alternative hypothesis is the development of paradoxical CSF acidosis during HD, which is aborted by slower dialysis.[143] Other implemented factors include intracerebral accumulation of endogenous osmotic solutes such as inositol, glutamine, and glutamate.[2]

Preventive measures include shorter and more frequent dialysis using small surface area dialyzers, hypernatric dialysate, reduction in blood flow, and individual intradialytic sodium modeling. Continuous mannitol infusions during dialysis or the prophylactic use of anticonvulsants are not recommended.

Seizures

HD-associated seizures are typically generalized an easily controlled. They occur in <10% of chronically dialyzed patients and may be more frequent in acutely dialyzed patients.[145] Focal neurological symptoms indicate a localized neurological disease such as an intracranial hemorrhage and warrant further evaluation. Other causes for seizures include DDS, uremic encephalopathy, acute aluminum intoxication, hypertensive encephalopathy, hypoglycemia, alcohol withdrawal, cerebral anoxia as a result of sustained intradialytic hypotension (i.e., from cardiac arrhythmias, hypersensitivity reaction, sepsis or hemorrhage), hyperosmolality as a result of hypernatremia, hypocalcemia, use of epileptogenic drugs (e.g., theophylline, meperidine, β-lactams), and intracerebral retention of radiocontrast agents. rHuEPO therapy has also been implicated as a cause for seizures during dialysis, typically in patients with preexisting hypertension.

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. Intravenous diazepam or clonazepam, and phenytoin may be required. Intravenous administration of 50% dextrose in water should be administered if hypoglycemia is suspected. In children with HD-associated seizures, the prophylactic use of diazepam appears to be more effective than phenobarbital.[146]

Acute Aluminum Neurotoxicity

Acute aluminum neurotoxicity may occur because of aluminum contamination of dialysate following administration of desferrioxamine resulting in higher aluminum levels. It may also follow the concomitant administration of oral aluminum-based phosphate binders and citrate compounds, which enhance aluminum absorption in the small intestine, and increase solubility and uptake of aluminum by the central nervous system.[147] The acute onset of this syndrome comprises agitation, confusion, seizures, myoclonic jerks, coma, and death. Plasma aluminum levels are typically >500 mcg/L, and highly suggestive EEG findings include multifocal bursts of slow or delta wave activity and frequent spikes. The CT scan is usually normal. Acute aluminum neurotoxicity of adult patients leads to death in most of the patients despite chelation therapy. Of note, the administration of low-dose (5 mg/kg) desferrioxamine 5 hours before the start of HD has been shown to be uneventful.[148]

The classical aluminum intoxication syndrome, though rare nowadays, has a more chronic course characterized by dementia, osteomalacia, microcytic anemia (in a small number of patients), and elevated plasma aluminum levels. This syndrome is now distinctly unusual because of contemporary water purification systems and the marked decline in the use of aluminum-containing phosphate binders.

HEMATOLOGICAL COMPLICATIONS

Leukopenia

Intradialytic leukopenia has been one of the earliest indices of poor membrane biocompatibility. The onset is usually rapid and peaks at 10–15 minutes.[149,150] Neutrophils and other granulocytes are primarily affected. The leukocyte count usually returns to normal by the end of dialysis and may exceed the predialysis values. This rebound leukocytosis has been ascribed in part to demargination of leukocytes from the vascular wall and from a recruitment of neutrophils from the bone marrow following an increase in circulating levels of granulocyte colony-stimulating factor.[151] Although granulocytes are readily seen on the dialyzer membrane surface under microscopy,[152,153] the disappearance of these cells from the circulation is primarily due to sequestration in the pulmonary vasculature. Pulmonary leukosequestration has been demonstrated using radiolabeled cells in clinical studies.[154] Binding of C5a to neutrophil cell-surface specific receptors is the primary underlying mechanism, and the degree of complement activation correlates closely with the degree of leukopenia.[155–157]

Intradialytic Hemolysis

Hemolysis associated with HD is rare (Table 24-4) and is most often caused by chemical contaminants, hypotonic or overheated dialysate,[158] or kink or manufacturing defects of the blood-line tubing.[51,158] Oxidative stress may also increase the red blood cell (RBC) membrane fragility through lipid peroxidation, resulting in hemolysis.[159]

TABLE 24-4 Causes of Intradialytic Hemolysis

MECHANISMS OF INJURY	ETIOLOGIES
Traumatic Fragmentation	- Dialyzer roller pump - Excessive suction at arterial access site - Single-needle dialysis - High blood flow through a small needle - Kinked dialysis catheter/tubing - Right atrial subclavian catheter
Thermal	- Overheated dialysate >47°C - Dialysate <35°C, activation of anti-N cold agglutinin (formaldehyde)
Osmolar	- Hypoosmolar dialysate - Hyperosmolar dialysate
Oxidative Injury	- Chloramines - Nitrite/nitrate - Copper - Drugs (quinine sulfate)
Reducing Injury	- Formaldehyde
Interference with Cellular Thiols	- Copper
Interference with Iron Uptake	- Aluminum
Inhibition of RBC Glycolysis	- Formaldehyde
G6PD* Deficiency	- Exacerbated by oxidants (quinine sulfate)
2, 3-DPG Deficiency**	- Hypophosphatemia
Drug-Induced Microangiopathy	- Quinine sulfate

*Glucose-6-phosphate dehydrogenase.
**2, 3-diphosphoglycera.

Whereas arterial limb negative pump pressures of less than −350 mmHg can cause mild hemolysis in a clinical setting,[160] in experimental studies, pressures as low as −720 mmHg failed to cause hemolysis.[161] The use of smaller gauge needles has been associated with significant hemolysis.[162] Other mechanical factors within the circuitry that may result in hemolysis include the varying geometry of the dialyzer inlet chamber.[163]

The most common chemical contaminants that cause hemolysis are chloramines, monochloramines, dichloramines, and trichloramines, which form when chlorine and ammonium are added to the municipal water supply as disinfectants.[164] These compounds can cause oxidative injury to RBC, resulting in methemoglobinemia and acute hemolysis.[165] Copper contamination leads to similar oxidative stress. Deionization and reverse osmosis do not effectively remove these contaminants. Adsorption through granular activated carbon[166] or neutralization of the dialysis fluid with ascorbic acid, a reducing compound, can prevent complications from chloramine.[165] The AAMI guidelines indicate a maximum chloramine content of 0.1 mg/L in dialysis water, compared to the 4 mg/L maximum concentration allowed in drinking water according to the Environmental Protection Agency (EPA).[167]

Nitrate and nitrite intoxication can occur in home HD patients who use well water contaminated with urine from domesticated animals, resulting in methemoglobinemia and hemolysis.[168] The AAMI guidelines recommend a maximum nitrate concentration of 2 mg/L for dialysis water,

compared to the 10 mg/L maximum concentration allowed in drinking water.[167]

The retention of formaldehyde and hydrogen peroxide during dialyzer reprocessing has been associated with hemolysis.[169,170] Formaldehyde is a potent reducing agent that impairs RBC metabolism by inhibiting glycolysis[169] and may act as a hapten that induces hemolysis by formaldehyde-induced anti-N-like cold agglutinins.[171]

Finally, drug-induced hemolysis particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, microangiopathic hemolytic anemia (e.g., quinine sulfate), hypophosphatemia, hypersplenism, and insufficient dialysis are rare causes that need to be considered.[165]

Patients with methemoglobinemia usually complain of nausea, vomiting, hypotension and cyanosis, and oxygen therapy does not improve black-colored blood present in the extracorporeal circuit. Copper contamination should be suspected in the presence of skin flushing, abdominal pain, and/or diarrhea.

The diagnosis of acute hemolysis is self-evident when grossly translucent hemolyzed blood is observed in the tubing. Evaluation should include reticulocyte count, haptoglobin, lactate dehydrogenase, blood smear for schistocytes or Heinz bodies, Coombs test, and measurement of methemoglobin. Bone marrow examination may occasionally be indicated. More importantly, analysis of tap water for chloramines and metal contaminants and thorough analysis of the dialysis procedure for clues of increased blood turbulence and mechanical RBC injury are recommended.

Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) has increasingly been recognized as an important clinical problem in dialysis patients. Type I HIT is characterized by the development of mild thrombocytopenia, where the platelet count rarely drops to less than 100,000/μl. Heparin can usually be continued and the thrombocytopenia resolves spontaneously. By contrast, type II HIT results in more severe thrombocytopenia, is IgG-antibody mediated,[172] and is characterized by arterial and venous thromboses and dialysis circuit clotting,[173] including a hemorrhagic propensity. The antibodies are directed against the complex of heparin and platelet factor IV.[174,175] Among chronic dialysis patients the prevalence of HIT is around 4%.[174,176]

The diagnosis of type II HIT is complex and depends on multiple criteria including the degree, rapidity and time of onset of thrombocytopenia, the presence of thrombosis, and resolution of the symptoms after cessation of heparin.[174,175] The presence of heparin antibodies only acts as an adjunct to the diagnosis.

The treatment of this syndrome includes complete withdrawal of all heparin products flush solutions and catheter locks, and the use of heparinoids such as argatroban or danaparoid,[177] or direct thrombin inhibitors such as lepirudin, a biosynthetic hirudin analogue. Of note, low molecular weight heparin is contraindicated. Lepirudin can be used as a 0.1–0.2 mg/kg IV bolus administered 5 minutes before starting HD, with a target activated prothrombin time of 1 hour into dialysis of 1.5–2 times normal.[178,179] Among patients with HIT who have indwelling dialysis catheters, at the end of dialysis, the venous and arterial ports of the catheter can be filled with lepirudin (1 mg/ml), according to the volumes indicated on the catheter.[180]

Transient thrombocytopenia may also result from blood-membrane interactions and reaches a nadir 1 hour after starting dialysis, with a platelet count declining to <100,000/mm^3.[156] Thrombocytopenia may also be secondary to other drugs used during dialysis such as vancomycin, quinine sulfate, or desferrioxamine.[181–183]

Hemorrhage

Bleeding complications are commonly related to anticoagulation. Heparin confounds the uremic bleeding tendency, which is due to platelet dysfunction, abnormal platelet-vessel wall interaction, altered blood rheology and platelet adhesion secondary to anemia, and abnormal production of nitric oxide.[184,185] An increased incidence of spontaneous bleeding episodes has been reported in HD patients, particularly bleeding at specific sites such as gastrointestinal arteriovenous malformation, colonic ulcers of the Dieulafoy-type, subdural hematoma, retroperitoneal bleeding, uremic hemopericardium, hemorrhagic pleural effusion, hemoptysis, subcapsular hepatic hematoma, ocular anterior chamber hemorrhage and skin hemorrhages including petechiae, ecchymosis, and subungual splinter hemorrhages.[2,91,186–188] Rupture of native, cystically transformed kidneys with retroperitoneal hematoma formation has also been described.[189]

Despite its limitations, the bleeding time is the best indicator of hemorrhagic tendency in dialysis patients. Local treatment of the hemorrhage and treatment/reversal of uremic platelet dysfunction are both needed. Strategies to achieve improvement in platelet function include an increase in rHuEPO dose or RBC transfusions to achieve a hematocrit >30% to improve rheological platelets-vessel wall interactions, intravenous conjugated estrogens at 0.6 mg/kg/day for 5 consecutive days, intravenous/subcutaneous 1-deamino-8-D-arginine vasopressin (DDAVP) at 0.3 mcg/kg over 15–30 minutes, and/or intravenous infusion of cryoprecipitate. For patients experiencing severe bleeding, particularly when related to anticoagulation, it is advisable to consider heparin-free dialysis, using normal saline flushes every 15–30 minutes with ultrafiltration adjustments,[190] regional heparin or citrate anticoagulation,[191] heparin modeling, or prostacyclin.[192] It is important to note that heparin-free dialysis may cause a stimulation of the coagulation system, increased fibrinogen consumption and accelerated dialyzer hollow fiber clotting.[193] The use of low-molecular weight heparin in HD has recently been proposed because of its convenient dosage regimen and lower impact on blood lipid levels, although bleeding complications are still possible.[194] Similarly, the use of lepirudin in dialysis patients with type II HIT has also been associated with bleeding complications.[195]

In patients scheduled to undergo elective surgery or invasive procedures, it is recommended that aspirin be stopped a week earlier, the dose of anticoagulants be reduced to minimum and hematocrit maintained above 30%. In some cases, DDAVP and/or estrogens may also be required.

PULMONARY COMPLICATIONS

Hypoxemia

Transient hypoxemia during HD occurs in up to 90% of patients and is defined by a drop in arterial PaO_2 by 5–30 mmHg, which reaches a nadir between 30 and 60 minutes, and returns to normal within 60–120 minutes following discontinuation of dialysis.[196] This mild reduction becomes clinically significant only when significant structural cardiopulmonary disease is present. The use of supplemental oxygen during dialysis improves arterial oxygen tension, but neither carbon dioxide tension nor breathing patterns are altered by this intervention.[197] Transient hypoxia is more common when dialyzers with high complement activating potential (unsubstituted cellulose) and acetate dialysate are used.[198,199] This may be mediated by complement activation following blood exposure to the free hydroxyl groups of cellulose membranes, with subsequent margination of leukocytes in the pulmonary vasculature.[2] Acetate dialysate may lead to loss of carbon dioxide in the dialyzer and thus result in hypocapnia and consequent compensatory hypoventilation. Use of bicarbonate dialysate (>35 mEq/L) may lead to hypoventilation and hypoxia by way of metabolic alkalosis.[2]

For diagnosing hypoxia during dialysis, arterial blood-line oxygen tension accurately correlates with systemic arterial blood and can conveniently be used in patients with an arteriovenous fistula or graft.[200]

Substituting acetate with bicarbonate dialysate at a concentration <37 mEq/L, intradialytic oxygen supplementation, particularly in high risk patients, maintaining optimal hematocrit values to maximize blood's oxygen carrying capacity and sequential ultrafiltration followed by HD, particularly in patients with fluid overload can ameliorate dialysis-associated hypoxemia. In addition, the use of dialyzers with lower complement activating potential such as synthetic, substituted cellulose, or reprocessed unsubstituted cellulose dialyzers could further reduce the likelihood of hypoxemia during HD. Finally, the use of cold dialysate may reduce intradialytic hypoxic episodes.[201]

TECHNICAL MALFUNCTIONS

Air Embolism

The incidence of air-embolism, a potentially fatal complication, has decreased significantly because of improvements in dialysis machine safety monitors. The segment of extracorporeal circuit that is most vulnerable to air entry is the prepump tubing segment, where significant subatmospheric pressures of up to 250 mmHg can occur. Air can also originate from intravenous infusions circuits, especially with glass bottled intravenous solutions, air bubbles from the dialysate, and central venous catheters.[202] Furthermore, the use of high blood flow rates may allow rapid entry of large volumes of air despite small leaks.

Clinical manifestations depend on the volume of air introduced, the site of introduction, the patient's position, and the speed at which air is introduced.[203] The volume of air required to produce clinical manifestations varies because of the previously mentioned factors and is partly dependent on preexisting cardiovascular or pulmonary disease. Microbubbles of air introduced at a slow rate dissolve in the blood and are better tolerated than macrobubbles. In the sitting position, air entry through a peripheral vein may bypass the heart and cause emboli into the cerebral circulation.[204] The acute onset of seizures and coma in the absence of precedent symptoms such as chest pain or dyspnea is highly suggestive of air embolism. If the patient is supine, air introduced through a central venous line will be trapped in the right ventricle where it forms foam, interfering with cardiac output, and, if large enough, lead to obstructive shock. Dissemination of microemboli into the pulmonary vasculature occurs. In this event, dyspnea, dry cough, chest tightness, or respiratory arrest can also occur. Further passage of air across the pulmonary capillary bed can lead to embolization to a major cerebral or coronary artery. Foam may be visible in the extracorporeal tubing, and cardiac auscultation reveals a peculiar churning sound. In the Trendelenburg position, air emboli migrate to the lower extremity venous circulation, resulting in ischemia, because of increased outflow resistance. Clinical manifestations include acrocyanosis, paresthesia and pain, and, unless peripheral vascular disease coexists, the outcome is usually favorable.

Once the diagnosis is suspected, the first step is to clamp the venous blood-line and stop the blood pump. For right heart air emboli, the patient is immediately placed in a recumbent position on the left side with the chest and head tilted downward. Cardiopulmonary support includes the administration of high-flow oxygen and endotracheal intubation and mechanical ventilation as needed. Aspiration of air from the ventricle by a percutaneously inserted needle or right atrial dialysis catheter can be attempted. If available, consideration should be given to hyperbaric oxygenation, where the patient undergoes decompression at a rate that allows the dissolved air to be expired through the lungs without coming out of solution.[205,206]

Preventive measures depend primarily on dialysis machines equipped with venous air bubble traps and foam detectors located just distal to the dialyzer and venous pressure monitor at the venous end. The detector is attached to a relay switch that simultaneously activates an alarm, shuts off the blood pump, and clamps the venous blood line if air is detected. Therefore, dialysis should never be performed in the presence of an inoperative air detection alarm system. Glass bottles containing intravenous solutions should be avoided because they create vacuum effects that can permit air entry into the extracorporeal system. Further, dialysis catheters should be aspirated for blood return and flushed with saline before connection. Dialyzers rinsing with saline should fill up all compartments and remove air bubbles. Finally, removing dissolved air, heating, and degassing of dialysis water, particularly in winter months, is accomplished by exposing heated water (34°C–39°C) to high negative pressure during the purification process.[207]

Blood Loss

Blood loss during HD can result from malfunction of the dialysis circuitry or internal or external hemorrhage of the patient that is caused or worsened by anticoagulation given during dialysis. The latter has been discussed previously.

Technical complications are arterial or venous needle disengagement, blood-line disconnection, femoral or central line dialysis catheter perforation or dislodgment, or rupture of a dialysis membrane with or without malfunction of the blood leak detector. Clinical findings include hypotension, loss of consciousness, and cardiac arrest, sometimes within minutes of starting HD.[208]

Blood loss can also occur following traumatic insertion of a dialysis catheter that results in a rapidly expanding, painful hematoma. Intrapericardial blood loss can lead to chest, shoulder, or neck pain;[209] back, flank, groin, or lower abdominal quadrant pain/distension can result from retroperitoneal bleeding.[210] Management of acute blood loss includes the immediate discontinuation of dialysis, pressure application for local hemostasis, hemodynamic support, and oxygen administration; a blood transfusion may be needed for severe blood loss.

Incorrect Dialysate Composition

Incorrect dialysate composition occurs as a result of technical or human errors. There are two types of dialysate solution delivery systems. With central delivery, the solution used for the whole dialysis unit is produced by one machine by mixing liquid concentrate with purified water and offers the advantage of reduced equipment and labor cost. With the individual system, each dialysis machine proportions its own dialysate liquid concentrate with purified water, permitting the modification of dialysate composition for a given patient. Because the primary solutes constituting the dialysate are electrolytes, the degree of dialysate concentration will be reflected by its electrical conductivity. Therefore, proper proportioning of concentrate-to-water can be achieved by a meter, which continuously measures the conductivity of the dialysate solution as it is being fed to the dialyzer. Life-threatening electrolyte and acid-base abnormalities are avoidable if the conductivity alarm is functioning properly and the alarm limits are set correctly. However, in dialysis machines that are equipped with conductivity-controlled mixing systems, the system automatically changes the mixing ratio of the concentrates until the dialysate solution conductivity falls within the set limits. This may inadvertently lead to dialysate without any bicarbonate, with apparently acceptable conductivity. Therefore, if conductivity-controlled systems are used, it is safer to also check the dialysate pH before dialysis. Conductivity monitors can fail or can be improperly adjusted because of human error. However, it is important to add human monitoring of dialysate composition before every treatment, whenever a machine has been sterilized, moved about, and whenever a new concentrate is used. Furthermore, many nonstandardized solutions are available, some of which may be used with an inappropriate proportioning system. Therefore, it is essential that the supplies match the machine-proportioning ratio for which they were prepared to obtain the appropriate final dialysate composition.

Dysnatremia

Because disturbances in renal water handling cannot occur in anephric dialysis patients, the etiology and management of dysnatremia is limited to factors related to dialysis and interdialytic fluid and electrolyte intake.

Hypernatremia

Hypernatremia can result from a faulty dialysate concentrate composition or an incorrect concentrate to water ratio, and dysfunction of conductivity monitors or alarms.[63] This results in water shifts from the intracellular to the extracellular fluid compartment and leads to cell shrinking. Symptoms include profound thirst, headache, nausea and vomiting, seizures, coma, and death.[186] Aggressive treatment is mandatory because mortality from acute severe hypernatremia (Na >160 mEq/L) is greater than 70%.[211] Management includes cessation of dialysis, hospitalization, and infusion of 5% dextrose in water and HD with a different dialysis machine, particularly if conductivity monitoring malfunction is suspected. The dialysate sodium level should be 2 mEq/L lower than the plasma and isotonic saline should be concurrently infused. Dialysis against a dialysate sodium level that is 3–5 mEq/L lower than plasma the level may increase the risk of disequilibrium. Ultrafiltration with equal volume replacement with normal saline is another option.

Hyponatremia

Failure to add concentrate, inadequate concentrate/water ratio, and conductivity monitor or alarm malfunction can cause hyponatremia. Hyponatremia can also occur during the course of dialysis with a proportioning system, if the concentrate container runs dry and the conductivity set limits are inappropriate. Acute hypoosmolality causes hemolysis with hyperkalemia and hemodilution of all plasma constituents because of massive transfer of water from dialysate in the blood, leading to water intoxication.[212] Symptoms include restlessness, anxiety, pain in the vein injected with the hypotonic hemolyzed blood, chest pain, headache, nausea, and occasional severe abdominal/lumbar cramps.[186] Pallor, vomiting, and seizures may be observed. Treatment of dialysis-induced hypoosmolality consists of clamping the blood lines and discarding the hemolyzed blood in the extracorporeal circuit. High-flow oxygen and cardiac monitoring because of hyperkalemia and potential myocardial injury are imperative.[186] Dialysis should be restarted without delay, with a new batch of dialysate, new dialyzer, and low dialysate potassium.[186] Anticonvulsants are indicated for seizures and blood transfusions may be needed for severe anemia.

The susceptibility of dialysis patients to complications is poorly understood because of the rapid correction of hyponatremia by dialysis against a high sodium dialysate. Transient urea dysequilibrium has been implied as a protective factor against cerebral water loss during rapid correction of extracellular osmolality during dialysis.[213] Even in the most acute symptomatic hyponatremic patient, a cautious approach is warranted, where a correction of sodium concentration by no more than 1–2 mEq/L/hr should be achieved.[214] Continuous renal replacement therapies have been used successfully for such a gradual correction of serum osmolality.[215]

Dyskalemias

Life-threatening hyperkalemia is not a common problem in dialysis patients, and if it occurs, is often caused by inadequate dialysis or dietary indiscretion. In healthy subjects,

the kidneys excrete over 90% of the daily dietary potassium load. Anuric dialysis patients are able to excrete significant amounts of potassium through extrarenal potassium excretion, primarily in the colon. This mode of excretion depends on the stool volume and is minimal if constipation exists.[216] The use of fludrocortisone, a synthetic mineralocorticoid, has been proposed for enhancing colonic potassium secretion.[217] Despite a typically low dialysate potassium concentration of 1–3 mEq/L, potassium removal is limited because of its large distribution in the intracellular compartment of over 90% of total body potassium. A quantitative study of potassium removal over 4 hours of dialysis with a 1-mEq/L dialysate potassium concentration in hyperkalemic (serum potassium level 5–6 mEq/L) patients resulted in a mean potassium removal of 107 mEq per treatment. However, the serum levels rose back to over 5 mEq/L after reaching a nadir of 3.5 mEq/L.[218] The findings confirm our current understanding of the kinetics of potassium removal by dialysis, which does not follow single pool kinetics because of the delayed release of intracellular potassium. This underscores the relative inefficiency of a high serum to dialysate potassium gradient and illustrates why the use of potassium-free dialysate should be discouraged. The latter may precipitate cardiac arrhythmias, reduce dialysis efficiency through arteriolar vasoconstriction and small solute compartmentalization, and limit correction of acidosis by impairing bicarbonate diffusion into the blood compartment.[219–221] Potassium modeling and longer HD treatments have been suggested to avoid severe rebound.[222] Finally, with regards to the effects of packed RBC (PRBC) transfusion on potassium balance, various studies suggest that the potassium load per unit of PRBC transfused is 5–7 mEq for units stored 14 and 21 days, respectively,[223] and therefore intradialytic PRBC transfusion should not be discouraged.

Severe hypokalemia induced by HD can occur despite the use of dialysate potassium concentration higher than serum.[224] This is due to rapid correction of acidosis that leads to the intracellular shift of potassium. Overall, unless significant losses as a result of vomiting, diarrhea or nasogastric suction are present, hypokalemia is not generally considered to be a problem in HD patients. Patients with marginal total body potassium stores (the result of gastrointestinal losses) and metabolic acidosis, however, are prone to life-threatening hypokalemia during HD; intradialytic potassium losses combined with intracellular shifts as a result of correction of acidosis may acutely precipitate life-threatening muscle weakness or cardiac arrhythmias, particularly in patients treated with digoxin.

Acid-Base Disturbances

HD patients have an alkali requirement of 240 mEq per treatment, taking into account daily acid generation and intradialytic losses of organic anions, which are bicarbonate precursors.[225] The physiology of acid base disturbances in anephric patients on dialysis differs from that in subjects with functioning kidneys and is primarily governed by dialysis.

Metabolic Acidosis

A decrease in serum bicarbonate of greater than 4 mEq/L suggests the presence of a new metabolic acidosis.[225] Although acute intradialytic metabolic acidosis can occur as a result of improper mixing of concentrates or failure of pH monitors,[226] other causes that need to be ruled out include diabetic or alcoholic ketoacidosis, lactic acidosis, toxic ingestions, increased protein catabolism, progressive loss of residual renal function, and dilutional acidosis.[225,227] A transient acidosis during the first hour of acetate dialysis as a result of intradialytic bicarbonate loss that has not yet been compensated for by the metabolism of acetate by muscle mitochondria[228] has been described.

The patients typically present with acute onset of hyperventilation during HD. Treatment of severe metabolic acidosis includes the correction of the underlying cause and administering dialysis with the appropriate dialysate concentrate. Although dialysate bicarbonate levels of 35–38 mEq/L are adequate in most circumstances, excessive correction of severe metabolic acidosis (bicarbonate <10 mEq/L), may lead to paradoxical acidification of the CSF and increased lactic acid formation by tissues.[228]

Metabolic Alkalosis

In anephric patients, elimination of excess base does not occur and the high concentration of bicarbonate in standard dialysate usually maintains the alkalosis. However, with acetate dialysis, net alkali loss will occur when plasma bicarbonate is greater than 26–28 mEq/L.[229] The presence of metabolic alkalosis is suggested by a rise in plasma bicarbonate by 4–5 mEq/L from its usual value.[229] A blood gas may be warranted to assess the respiratory response. The most common cause of metabolic alkalosis in HD patients is hydrochloric acid loss as a result of vomiting or nasogastric suction and is usually seen in the intensive care unit setting or endogenous and exogenous sources of added alkali. Such alkali or alkali precursors include sodium bicarbonate, calcium carbonate or acetate, citrate (blood products), lemon consumption, alkalinizing agents, lactate (Ringer solution), acetate (total parenteral nutrition solutions), and connection of the bicarbonate concentrate to the wrong port.[229,230] The combination of sodium polystyrene sulfonate and aluminum hydroxide can lead to absorption of alkali that is normally neutralized in the small intestine.[231] Usually, removal of the alkali source is sufficient, and H_2-receptor antagonist or gastric H^+/K^+ ATPase inhibitors may be successful if gastric acid loss is present. If dialytic support is required for the rapid correction of this acid-base disorder, the dialysate composition may be altered by replacing alkali with chloride,[232] substituting bicarbonate with acetate dialysate,[233] using acid dialysate,[234] or using hydrochloric acid infusion during dialysis with citrate dialysis.[235] Use of conventional or lower dialysate bicarbonate level (25–30 mEq/L) is probably as effective.[236]

Severe metabolic alkalosis as a result of HD is rare and may be caused by an error in dialysate concentrates,[237] reversed connection of bicarbonate and acid concentrate containers to the entry ports of the dialysis machine,[238] or malfunction of the pH monitor. Furthermore, severe metabolic alkalosis can occur with regional citrate HD[239] and following continuous renal replacement therapies in the setting of acute renal failure (ARF).[240,241]

Respiratory Alkalosis

Due to the lack of a renal compensatory response,[229] acute respiratory acid-base disorders are more likely to cause mixed acid-base disorders that may be severe and life threatening.

During HD, despite losses of carbon dioxide into the dialysate, respiratory alkalosis does not occur.[242] However, anxiety, stroke, sepsis, and hepatic failure or pregnancy may be precipitating factors for hyperventilation and result in respiratory alkalosis. A hyperventilation syndrome has been described in a patient on continuous ambulatory peritoneal dialysis (CAPD), which disappeared once the patient was switched over to HD.[243]

Respiratory Acidosis

The concomitance of respiratory acidosis and renal failure is common in the intensive care unit setting. REDY sorbent dialysis is a dialysate regenerating system, requiring only 6 L of dialysate compared to 120 L for a standard 4-hour dialysis treatment.[244] The system contains a sorbent cartridge that has three different layers that participate in the detoxification process. Although it offers some advantages over HD, REDY sorbent dialysis can cause acute hypercapnia.[245] Indeed, during dialysate regeneration, the breakdown of urea by urease that occurs in the second layer generates NH_4^+ and HCO_3^-.The third layer consisting of zirconium phosphate is a cation exchanger that exchanges Na^+ and H^+ for NH_4^+. Hence carbonic acid is formed when HCO_3^- combines with H^+. Although the lungs would normally eliminate the carbon dioxide, retention may occur in patients with underlying pulmonary disease, resulting in hypercapnia and a superimposed or worsening respiratory acidosis.[244]

Last, despite the theoretical possibility of a decrease in respiratory drive as a result of bicarbonate supplementation during dialysis, a study of intubated patients with ARF who were undergoing HD showed that the decrease in respiratory drive correlated with the ultrafiltration volume rather than with the reversal of the metabolic acidosis.[246]

Chemical Contaminants

The *"hard water syndrome"* used to occur when untreated tap water containing high levels of dissolved minerals was used for dialysate preparation. It manifests an hour after start of dialysis, and symptoms include nausea, vomiting, hypertension, extreme weakness and lethargy (as a result of hypercalcemia), and a warm sensation to the skin (as a result of hypermagnesemia).[247] Acute pancreatitis may be observed.[248] Currently the water used for dialysate preparation is treated with deionization and reverse osmosis to control levels of divalent cations and remove trace elements that may be present. However, in some rural areas, the mineral content of the water is very high, and the hard water syndrome can occur during home HD despite seemingly adequate pretreatment of the water source.[249] The diagnosis is confirmed by establishing elevated dialysate water calcium and magnesium levels. Treatment is supportive and dialysis should be stopped and restarted with properly treated water.

Metal contaminants that induce acute hemolysis include copper, zinc, and aluminum (see Intradialytic Hemolysis). Intoxications with other metals such as lead and nickel may also occur.[186] Fluoride is a trace element that may accumulate in HD patients and deposit in bone.[250,251] However, its contribution to renal osteodystrophy is unclear.

When dialysate water purification is based on deionizing (DI) systems using ion exchange resins, fluoride contamination of dialysate can occur once DI columns are exhausted. Acute fluoride poisoning may follow, manifesting primarily by gastrointestinal symptoms and life-threatening hyperkalemia caused by a potassium channel blockade, leading to significant extracellular potassium leakage.[252] A case of acute fluoride poisoning that occurred in a dialysis unit in Illinois in 1993 was reported to the CDC.[13] DI systems were used during unit remodeling when the incident occurred. Periodic testing of dialysis water supply for fluoride content, maintenance of, and familiarity of the healthcare team with DI systems are necessary to prevent these events.

Temperature Monitor Malfunction

Heating of the dialysate assists in the degassing and improves the mixing of water with dialysate concentrate. The internal controls of the thermostat are set up by the manufacturer to limit the dialysate temperature to 33°–39°C. Malfunction of the thermostat in the dialysis machine can result in the production of excessively cool or hot dialysate. Accidental use of cool dialysate is not dangerous and has beneficial hemodynamic effects, although it may cause shivering and/or hypothermia. Overheated dialysate, especially when temperatures above 51°C are reached, can cause immediate hemolysis and life-threatening hyperkalemia.[186] Lower temperatures of 47°–51°C may cause an up to 48-hour delay in the onset of hemolysis.[253]

If the dialysate temperature rises to 51°C, dialysis must be stopped immediately and the blood in the system discarded. The patient should be monitored and treated for hyperkalemia and transfused as necessary. Dialysis may be resumed to treat hyperkalemia and to cool the patient by using a dialysate temperature of 34°C. To prevent this potentially catastrophic complication, visual and audible alarms are mandatory, as is a dialysate bypass for drainage, required with high-temperature alarms.

Milder thermal imbalances may be caused or worsened by ultrafiltration such that a reduction in blood volume has to be accompanied by relative cooling to achieve thermal energy homeostasis and avoid heat accumulation.[254]

MISCELLANEOUS COMPLICATIONS

Postdialysis Fatigue Syndrome

Common nonspecific symptoms of fatigue and malaise are observed in about 33% of patients.[208,255] The incidence of this syndrome has decreased since glucose-free acetate-containing solutions were replaced by glucose/bicarbonate dialysate.[256] Reduced cardiac output, peripheral vascular disease, depression, poor conditioning, postdialysis hypokalemia or hypoglycemia, mild uremic encephalopathy, neuropathy

or myopathy and blood membrane interactions may be contributing factors. Randomized, double blind, controlled studies failed to show improvement by exchange of cuprophane with PS membranes[257,258] but showed that high ultrafiltration rates and low dialysate sodium concentration predispose to postdialysis fatigue.[259] On-line predilution hemofiltration has been shown to be more effective than ultrapure high-flux HD.[260] Malaise has also been ascribed to carnitine deficiency, which is important for muscle metabolism, and L-carnitine supplementation has been shown to improve postdialysis well-being.[65] More frequent, modalities, such as short daily or nocturnal dialysis, may allow patients to recover faster from postdialysis fatigue.[261]

Pruritus

Pruritus is a common symptom among dialysis patients and is often multifactorial in origin and difficult to treat. Xerosis, hypercalcemia and hyperphosphatemia (resulting in calcium phosphate crystal deposition in the skin), hyperparathyroidism, inadequate dialysis,[262] and female gender[263] are all risk factors for this vexing problem. Some but not all studies have observed elevated plasma histamine and serotonin levels and increased mast cell proliferation in the skin.[264] Of note, use of an antihistamine agent or a 5-HT3-receptor antagonist does not affect these levels.[264] Two clinical trials failed to demonstrate any benefit from the use of ondansetron for pruritus in dialysis patients.[265,266]

In many cases, pruritus is more severe during or after dialysis and may be an allergic manifestation to heparin, ETO, formaldehyde, or acetate.[27] The exchange of formaldehyde as the germicide during reuse and the use of gamma-sterilized dialyzers and switching over to bicarbonate dialysate have been associated with cessation of itching.[27] Anecdotal reports suggest a likelihood of itching with cuprophane and new dialyzers compared to substituted cellulose and reused dialyzers.[208] Eczematous reactions to antiseptic solutions used to clean the vascular access site, rubber glove components (thiuram), nickel in the puncture needles, epoxy of the glue at the tube-needle joint, or the cellophane of glues used to maintain needles should be considered.[267]

Therapeutic strategies include the use of emollients and antihistamine agents, oral activated charcoal, ultraviolet therapy and sunbathing, ketotifen (a mast cell stabilizer), rHuEPO therapy, topical capsaicin,[268,269] essential fatty acid replacement,[270] and short-term use of daily oral naltrexone.[271] Finally, the dialysis prescription and adequacy should always be assessed.

Priapism

Priapism occurs either during or 2–7 hours following dialysis in about 0.5% of male patients[272] and is characterized by a painful erection that is unrelated to sexual activity. A causal relationship to an increase in blood viscosity as a result of heparin[273,274] high hematocrit, rHuEPO[275] and androgen therapy,[276,277] dialysis-induced hypoxemia, hypovolemia as a result of excessive ultrafiltration, particularly in black males with sickle cell trait,[272] and the use of prazosin[278] have all been implicated in the pathogenesis of this condition. Treatment includes immediate aspiration and irrigation of the corpora cavernosa.[279] Metaraminol has been used for irrigation in one report.[280] A dorsal penile block with 1% Xylocaine without epinephrine and intravenous sedation can be given for pain control, but opiates are also effective. Surgical treatment consists of creating a shunt for drainage of the corpora cavernosa.[279] Permanent erectile dysfunction frequently results but can be treated with implantable cavernosal prostheses.[186]

Hearing and Visual Loss

The exact role of HD in hearing disturbances is unclear. Hearing loss in HD patients has been reported.[281,282] One study reported a hearing loss incidence of 41%, 15%, and 53% in the low, middle, and high frequency ranges, respectively.[283] In the same study, the low frequency hearing improved in 38%, and worsened in 10% of patients after a single dialysis session.[283] Hearing impairment may improve following transplantation.[284] Advanced age, elevated plasma viscosity, and prior gentamicin administration are confounding factors of high frequency loss.[283] However, more recent investigations showed no acute change in audiometric parameters after HD but demonstrated a higher prevalence of hearing loss in patients with chronic kidney failure.[285,286] Acute hearing loss during HD may be the result of bleeding in the inner ear as a consequence of heparinization or hair cell injury of the cochlea from edema (endolymphatic hydrops).[186] Finally, ototoxicity has been reported following desferrioxamine therapy,[287] isoniazid,[288] and amikacin.[289]

Visual loss is rare during HD and may be caused by central retinal vein occlusion,[290] precipitation of acute glaucoma,[291] ischemic optic neuropathy associated with intradialytic hypotension,[292,293] or Purtscher like retinopathy caused by leukoembolization.[294] Desferrioxamine also causes ocular toxicity, and serial audiovisual monitoring may be required with chronic chelation therapy.[287]

Last, intradialytic visual and hearing impairment can occur following exposure to aged dialyzers with microembolization of cellulose acetate degradation products.[50]

Digoxin Toxicity

HD patients are particularly prone to complications associated with the use of digoxin (see Cardiac Arrhythmias). This compound has a narrow therapeutic window, and despite careful monitoring of drug levels, digoxin-induced arrhythmias can occur especially when coexistent with hypercalcemia, hypokalemia, and hypomagnesemia. A syndrome consisting of recurrent abdominal pain associated with use of digoxin can occur shortly after dialysis, particularly following marked ultrafiltration, and has been ascribed to digoxin-induced transient mesenteric ischemia.[292] Once digoxin intoxication has occurred, hemoperfusion with charcoal and antidigoxin antibodies are necessary for treatment as a result of inadequate clearance by dialysis. Adequate digoxin clearance of 145 ml/min has been achieved using a commercially available beta$_2$-microglobulin adsorption column (Lixelle, BM-01).[295]

A full list of references are available at www.expertconsult.com.

Chapter 25

FREQUENT HEMODIALYSIS: PHYSIOLOGICAL, EPIDEMIOLOGICAL, AND PRACTICAL ASPECTS

Rita S. Suri, M.D. and Alan S. Kliger, M.D.

INTRODUCTION

End-stage renal disease (ESRD) is a debilitating condition that results in impaired quality of life, significant morbidity, and premature death.[1–6] The majority of patients with ESRD receive renal replacement therapy in the form of conventional hemodialysis (HD), delivered 3 days per week for 3–5 hours per session, or peritoneal dialysis (PD). Despite advances in technology and in medical care, however, U.S. mortality rates on conventional HD and PD have changed little in the last decade, remaining at around 20% annually.[6] This chapter examines efforts to improve outcomes using more frequent HD regimens.

DEFINITION OF TERMS

Several terms have been used to describe the various frequent HD regimens, including "*short-daily*," "*daily*," "*nocturnal*," "*daily-nocturnal*," "*quotidian*," "*hemeral*," "*long*," "*intensive*," and "*alternative*." Here we refer to "*frequent HD*" as the delivery of at least five HD treatments per week. Frequent HD is typically delivered either during the day as short sessions, lasting 1.5–3 hours ("*short-daily HD*"), or at night for 6 or more hours while the patient sleeps ("*nocturnal HD*"). These treatments may be performed either in-center or at home, although short-daily HD is most commonly performed in-center, and frequent nocturnal HD is almost always done at home (Table 25-1).

Another alternative HD regimen that has been gaining increasing popularity is what we will refer to as "*long conventional HD*." Also called "*extended hours HD*," this regimen is performed for 6–8 hours, three to four times per week. Although typically done at night, either in-center or at home, the famous Tassin center in France has been offering this therapy during the day for over 3 decades with apparently good compliance.[7,8] Several for-profit dialysis centers in the United States currently practice this regimen 3 nights per week in-center, and it has been recently gaining popularity at other centers around the world as well.[9–14]

Finally, an increasing number of centers in the United States have been offering a form of HD delivered by a specific device called the NxStage System One. Because this HD treatment is performed nightly, some may think of this therapy in the same category as frequent HD. However, unlike frequent or extended hours HD that provide substantially greater small solute clearances than conventional HD and PD, the NxStage System One delivers more modest small solute

TABLE 25-1 Definition of Terms

Frequent Hemodialysis
• ≥5 sessions per week
Short-Daily Hemodialysis (SDHD)
• 1.5–3 hours per session, 5-7 days per week • Can be done either at home or in-center
Nocturnal Hemodialysis (NHD)
• ≥6 hours per session, 5-7 nights per week • Usually done at home
Long Conventional or Extended Hours Hemodialysis
• ≥6 hours per session, 3-4 nights per week (can be on every other night) • Can be done either in-center or at home • Some centers (e.g., Tassin) offer this therapy during the day

clearance because it uses low dialysate volumes.[15] This chapter will focus on frequent HD (short-daily and nocturnal) and extended hours HD. However, the issues discussed in the chapter do not necessarily pertain to the NxStage System One.

HISTORY OF FREQUENT AND EXTENDED HOURS HEMODIALYSIS

When HD was first introduced in 1960, there was no standard time or frequency. Patients were dialyzed for 8–15 hours once, twice, or thrice weekly, depending on the clinical status of the patient and physician preference. Soon after, thrice weekly HD became most widely accepted because it was found that patients generally felt better than with less frequent treatments. It should be noted that in that era, dialyzers were "*low efficiency*," delivering around 100 ml/min urea clearance, and thus long treatments of at least 8 hours were the rule. HD was offered only to a select few, and approximately half of all patients dialyzed at home.

In 1969, de Palma published the first report of daily hemodialysis.[16] He switched patients dialyzing for 8 hours 3 days per week, to 4–5 hours 5 days per week with notable improvements in urea clearance. Scattered reports with favorable results followed,[17–22] but daily dialysis never became common. Resource and cost constraints, along with the advent of high-efficiency dialyzers with high urea clearances, and volumetric machines that allowed rapid ultrafiltration, fueled the adoption of shortened, thrice weekly treatments. HD could now be offered to thousands of patients neatly slotted into one of three, 4-hour shifts during the day in in-center units. Long-hour treatments and home HD were essentially abandoned in North America and most of the world.

During the 1980s, short-daily dialysis was offered in a handful of centers in Europe,[23–26] and extended hours three times weekly HD continued to be practiced in France.[27] However, long hours, 6 nights per week HD was not introduced until the next decade. The late Robert Uldall is credited with starting the first nocturnal HD program in Toronto in 1994.[28] Andreas Pierratos, who took over the program after Uldall's death, reported improved quality of life, anemia, phosphate levels, and blood pressure control in these 13 patients after 3 years of follow-up.[29] In the next decade, short daily and nocturnal programs began sprouting up world wide, and today dozens of centers offer frequent HD. Recently, extended hours conventional HD has also become increasingly popular, particularly in centers that can offer this regimen in-center at night.[11] Although a growing trend, these regimens are by no means mainstream and are currently being used by <1% of patients receiving HD in North America.[30]

PHYSIOLOGICAL RATIONALE FOR FREQUENT AND EXTENDED HOURS HEMODIALYSIS

Improved "*Unphysiology*"

With conventional HD, the concentration of solutes falls and rises in a saw-tooth pattern. Termed the "*unphysiology*" of intermittent HD by Dr. C. Kjellstrand, these fluctuations are thought to contribute to uremic symptoms, poor quality of life, and adverse outcomes on HD.[31,32] With increased HD frequency, the interdialytic interval is shortened, resulting in less fluctuations in blood solute concentrations (Figure 25-1).[33] This potential improvement in unphysiology has been hypothesized to be one of the many potential benefits of frequent HD.[32]

Increased Clearance of Small Nitrogenous Solutes

Retention of water soluble nitrogenous wastes of <500 Da molecular weight (small solutes) is a major component of the uremic syndrome.[34] These molecules may lead to anorexia and malnutrition, fatigue, cognitive impairment, and depression. The suboptimal clearance of small solutes on conventional HD is improved with both short-daily and nocturnal HD, with resultant falls in time averaged blood solute concentrations.[35,36] This point is best understood with a discussion of urea kinetics.

The removal of urea and other small solutes by HD follows first-order kinetics. That is, for small solutes, the rate

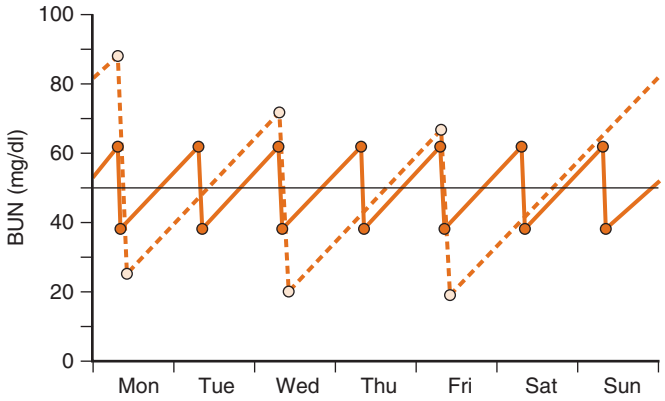


FIGURE 25-1 Weekly BUN profile in a single patient dialyzed according to different schedules. The solid saw-tooth line represents daily dialysis, the dotted line represents standard thrice weekly dialysis, and the solid horizontal line represents continuous dialysis. In all three cases, the time average blood urea nitrogen (BUN) is maintained at 50 mg/dl. (Data from T.A. Depner, Will daily home hemodialysis be an important future therapy for end-stage renal disease? Semin. Dial. 8(5) (1995) 266–268.)

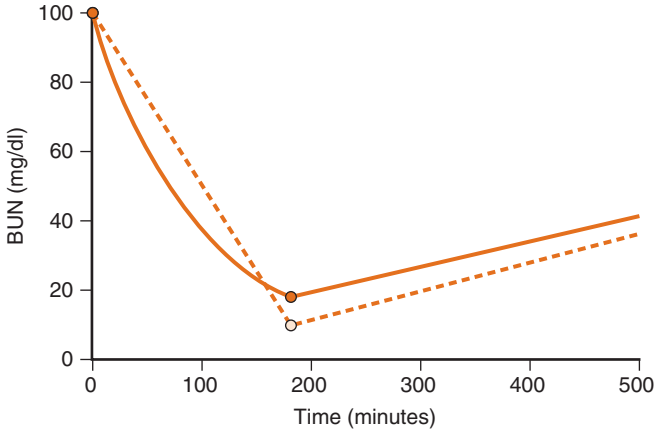


FIGURE 25-2 First order kinetics of urea removal. The rate of urea removal is proportional to the instantaneous urea concentration, as indicated by the solid line. This results in less solute removal than a theoretical dialysis in which urea removal is constant *(dotted line—zero order kinetic)*. Single compartment, fixed volume model. (Data from T.A. Depner, Benefits of more frequent dialysis: lower TAC at the same Kt/V, Nephrol. Dial. Transplant. 13 (Suppl. 6) (1998) 20–24.)

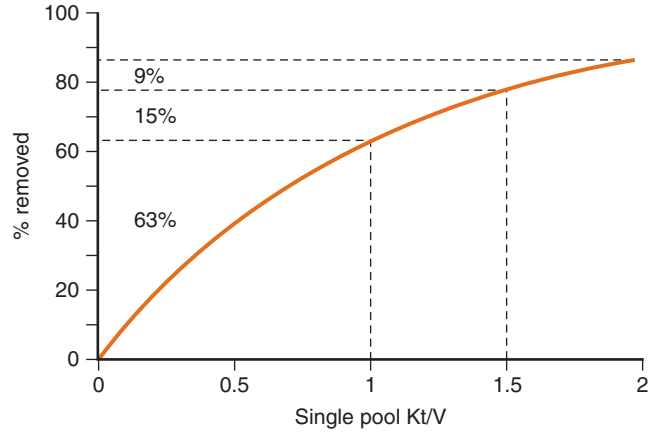


FIGURE 25-3 Relationship between total solute removal and dialysis session time, as represented by spKt/V. The rate of solute removal decreases as session time increases. Percentages shown are the incremental removals associated with an increase in time between the dotted lines. (Data from T.A. Depner, Assessing adequacy of hemodialysis: urea modeling, kidney Int. 45(5) (1994) 1522–1535.)

of removal with HD is proportional to the instantaneous blood concentration (Figure 25-2).[35] Consequently, most small solute removal occurs at the start of HD, with decreasing removal rates as the HD session proceeds. During the last hour of a 4.5 hour HD session, relatively little solute is removed in comparison to the first 3 hours (Figure 25-3).[37] Thus increasing HD session time on conventional HD results in minimal increments in total small solute removal. This is one hypothesis explaining why the recent landmark HEMO study failed to demonstrate improved outcomes with higher clearances on conventional HD. In this trial, the higher dose was achieved mainly by lengthening treatment times by around 30 minutes.[38]

With short-daily HD however, more time is spent dialyzing on the early, steepest part of the urea removal curve. This allows substantially greater weekly urea removal compared to conventional HD, despite similar weekly treatment times (9–12 hours in most cases). We have previously shown that short-daily HD results in up to 50% increase in weekly clearances, as measured by weekly std Kt/V urea (note this applies to short-daily HD delivered with conventional HD machines, not with the NxStage System One).[39]

Another problem with conventional HD is that as soon as the HD session is completed, the concentrations of urea and other small solutes rise again immediately, or "rebound".[40] During HD, only the blood compartment is exposed to the dialyzer. However, small solutes such as urea are widely distributed in cells and interstitial tissues. During dialysis, solutes must move from the interstitial and intracellular spaces into the blood compartment, where they then move through the dialyzer membrane. Although small nitrogenous solutes like urea transfer easily across cell membranes, the transfer is not immediate. It may take up to 60–120 minutes after the HD session is finished for complete equilibration between compartments to occur. Blood concentration of these solutes will increase (or "*rebound*") until they acquire equilibrium. As a result, clearance calculations using urea values measured at the end of the HD session before equilibration has occurred will overestimate the true total body clearance of urea.

When dialysis session time is increased to 6–8 hours, rebound is minimized. In other words, the entire volume of distribution of urea becomes available for removal during the HD session. With long conventional HD of 7–8 hours, 3 days per week, weekly small solute clearance can be increased by about 30% compared to conventional HD.[8,9] Nocturnal HD, which combines long times and higher frequency, provides weekly clearances that are double those of conventional HD and approximately 30%-50% more than with short-daily HD.[39] It should be noted that these increases occurred despite the use of significantly lower blood and dialysate flows with nocturnal HD in this study.[39]

Improved Ultrafiltration and Attainment of Target Weight

Patients on conventional HD become fluid overloaded as the sodium and water they consume during the interdialytic interval are retained. During the HD session, rapid fluid removal (ultrafiltration) may cause acute intravascular volume depletion, potentially resulting in intradialytic hypotension, cramping, and reduced quality of life.[41] Patients with intradialytic symptoms often fail to reach their fluid removal targets, contributing to hypertension, left ventricular hypertrophy, heart failure, and possibly death.[42–44]

It has been shown that hemodialysis patients with the highest ultrafiltration rates (i.e., interdialytic weight gain divided by treatment time) are not only most prone to intradialytic hypotension but also have the poorest survival.[45,46] Although the association between high ultrafiltration rates and survival may not be causal, lowering the ultrafiltration rate by increasing time from 4 to 5 hours was demonstrated to improve intradialytic symptoms in a randomized trial.[47] With long conventional or nocturnal HD, session time is lengthened to >6 hours, allowing a further reduction in the ultrafiltration rate and perhaps better refilling of the blood compartment from the interstitial space.[44] The potential result is less intradialytic symptoms, ease of ultrafiltration, successful achievement of target dry weight, and improved cardiovascular outcomes. The famous Tassin center in France, which dialyzes patients for 7–8 hours for 3 days per week, has

achieved high rates of normotension in its population without the use of antihypertensive medications for more than 3 decades.[8] Similarly, improvements in blood pressure, left ventricular hypertrophy, and intradialytic symptoms have been reported with nocturnal HD.[48,49] However, not all studies report concomitant reductions in extracellular fluid volume, suggesting that other mechanisms, including reduced peripheral resistance, likely play a role.[48]

Ultrafiltration rates are not reduced with short-daily HD because weekly time is not substantially higher than with conventional HD, and interdialytic fluid intake often increases. Yet short-daily HD has also been shown to consistently improve blood pressure.[50] One possible explanation is that the absolute amount of fluid removal is halved during the HD session with short-daily HD, allowing better tolerability of ultrafiltration and attainment of dry weight. Whether the reductions in peripheral resistance observed for nocturnal HD also occur with short-daily HD is unclear.

Increased Clearance of Middle Molecules and Phosphate

It is likely that the uremic syndrome is the result of accumulation of more than just small nitrogenous solutes.[51] Middle molecules in the 500–60,000 Da range, such as beta-2 microglobulin, cytokines, and complement, may be important uremic toxins.[52] Phosphate, although of small molecular weight, transfers poorly across cell membranes and thus behaves more like a middle molecule during HD than a small solute.[53,54] Beta-2 microglobulin has been implicated in the pathogenesis of dialysis amyloidosis,[55] and HD patients with high C-reactive protein and interleukin-6 levels are at increased risk of premature death.[56,57] High phosphate concentrations are associated with vascular calcification and increased mortality risk.[58–61]

The clearance of middle molecules and phosphate is time dependent.[54,62] Like small solutes, rate of removal of these molecules is maximal during the first 2 hours of standard dialysis. However, little is removed thereafter because of the extremely slow transfer from the intracellular to blood compartments. Longer HD sessions, which allow more time for middle molecule and phosphate movement out of cells, would be expected to improve removal of these molecules. Simulation studies show this to be the case,[63–66] and empirical data are available for phosphate.[67] Long conventional HD allows somewhat better achievement of phosphate targets,[68] but the removal of phosphate with nocturnal HD is considerably greater, such that some patients on nocturnal HD have been able to discontinue phosphate binders altogether.[69] On the other hand, short-daily HD does not result in marked improvement in weekly phosphate removal or hyperphosphatemia unless session time is at least 3 hours.[70]

REVIEW OF THE EVIDENCE REGARDING FREQUENT AND LONG CONVENTIONAL HEMODIALYSIS

Over the last 2 decades, the number of studies examining the effects of frequent and long conventional HD has exploded. In this section, we review the empiric evidence with respect to the efficacy and potential risks of these therapies. We also elaborate on ongoing research initiatives.

Efficacy

Short-Daily Hemodialysis

Using established methodology, we conducted a systematic review of the literature on short-daily HD.[50] Citations were identified in MEDLINE and EMBASE using validated search strategies. Dialysis journals that were not indexed and bibliographies of relevant articles were hand-searched, and two authors reviewed all citations. Articles that reported original data on five or more adults who were receiving short-daily HD (1.5 to 3 hours, 5 to 7 days per week) for at least 3 months were included.

We found 25 articles from 21 centers in eight countries describing 14 cohorts of 268 patients receiving short-daily HD over the period 1998 to May 31, 2005. Findings varied considerably among studies with respect to most outcomes, but two findings were relatively consistent. Decreases in systolic or mean arterial BP were reported in 10 of 11 studies,[71–80] whereas six of eight studies found no statistically significant change in phosphate or phosphate binder dose with short-daily HD at 3 to 24 months of follow-up.[76,81–85] In keeping with this, Ayus and colleagues found that phosphate control is only improved with short-daily HD if treatment time is extended beyond 3 hours.[70] Improvements were seen in hematocrit, hemoglobin, and/or erythropoietin dose in 7 of 11 studies.[71–73,77,79–81] Albumin increased in 5 of 10 studies.[71,73,80,86,87] Weekly interdialytic weight gain generally increased. Health-related quality of life improved in some studies but not in others. Left ventricular mass index significantly decreased in the one randomized crossover trial.[74]

The findings of these studies must be interpreted with caution because these studies had significant design limitations.[50] The number of patients per cohort was small, ranging from 5 to 72 (median 23), and follow-up was limited to 12 months for most studies. All studies except one were observational, and >75% of these had an uncontrolled pre-post design. There was only one randomized crossover trial of 12 patients followed for 6 months.[74]

There were also significant differences in the patients receiving short-daily HD in these studies compared to the general HD population.[50] Patients on short-daily HD were younger (mean age 41 to 64 years), had received dialysis for many years (2 to 11 years), and very few had diabetes (0% to 28%). Moreover, >50% of patients were dialyzed at home, suggesting a highly motivated, high functioning group. Thus whether the results from these studies can be extrapolated to the general HD population is uncertain.

Since the systematic review was published, there have been several additional small observational studies, also examining surrogate outcomes, with similar findings.[88–92] However, studies examining hard endpoints, such as hospitalizations, cardiovascular events, and survival have been almost nonexistent. In 2003, Ting and colleagues published their experience of 31 patients receiving short-daily HD for 1–6 years.[71] They found that compared to baseline, this cohort's hospitalization rate was reduced by ~35% on

short-daily HD. However, these results are likely affected by survivor bias. During the baseline period, all 31 patients' hospitalizations were counted for the year on conventional HD before their switch to short-daily HD, but during the 1–6 years of follow-up on short-daily HD, hospitalizations could be counted for surviving patients only. By the third year, there were only 15 patients remaining in the cohort, and by the sixth year, there were only four. It is likely that the most ill patients with the highest baseline hospitalization rates died. Thus the hospitalization rate would naturally decrease over time as these patients were eliminated from the cohort.

There has been only one study comparing survival on short-daily HD to conventional HD. Kjellstrand and colleagues studied 415 patients over the period of 1982–2005 from several countries; approximately one-third were from the United States, whereas the remaining were from Italy, France, and the United Kingdom.[93] They found that the 5-year survival of their short-daily HD cohort was significantly improved over that of in-center conventional HD patients as published by the United States Renal Data System (USRDS) Registry. The most concerning problem with this study, however, is that they did not adjust for several confounding factors. Patients receiving short-daily HD were matched to in-center conventional HD patients by age, sex, race, and primary renal diagnosis only. Comorbidities and the number of years on dialysis were not considered. The short-daily HD patients had been receiving HD for 5 ± 5.7 years (median 2.4 years, range 0 to 31), whereas those on conventional HD were a cohort of incident patients. In previous decades, incident cohorts had a worse prognosis than survivors who have been receiving dialysis for many years.[94] Moreover, almost two-thirds of those receiving short-daily HD in this study dialyzed at home; the comparator cohort received conventional HD in-center. These data suggest that those receiving short-daily HD may have been a healthier group of patients than those receiving in-center conventional HD. Thus the observed differences in survival could potentially be attributed to factors other than frequent HD in this study.

Nocturnal Hemodialysis

In 2005, a group from Calgary, Canada, published a systematic review of nocturnal HD.[95] They found 10 full text articles and four abstracts from four programs in Canada and the United States. Study sample size ranged from five to 63; follow-up ranged from 6 weeks to 3.4 years. There were no randomized trials or studies examining hard endpoints identified. Patient characteristics were not reported in this review.

There were statistically significant or trends toward improved control of hypertension in all seven studies that examined this outcome, with reductions in antihypertensive use and/or blood pressure. It has been previously suggested that these improvements may be the result of reduced total peripheral resistance and restoration of endothelium-dependent vasodilation with nocturnal HD.[48,96] Five studies examined phosphate control. All showed significant or nonsignificant trends towards to reductions in serum phosphate or need for phosphate binders with nocturnal HD. Some have in fact reported the need for dialysate phosphate supplementation with nocturnal HD. Nocturnal HD improved anemia in some but not all studies. An interesting in vitro study showed that the growth of erythropoeitic colony forming units is significantly improved when incubated with the serum of patients on nocturnal HD compared to serum from patients on conventional HD.[97] The effects of nocturnal HD on health-related quality of life measures were also variable.

This review was limited to blood pressure control, mineral metabolism, anemia, and health-related quality of life. However, other studies have suggested improvements in other outcomes with nocturnal HD. Improvements in exercise capacity,[98] open angle glaucoma,[99] and sleep apnea[100] have been observed. The mechanism of the latter may be related to an increase in pharyngeal cross-sectional area.[101] Resolution of calciphylaxis has also been reported,[102] including the potential stabilization of coronary calcification.[103] Pregnancy outcomes may also be better with nocturnal HD.[104]

To date, there has been a single published randomized trial comparing nocturnal to conventional HD. Culleton and colleagues randomized 51 patients receiving conventional HD to continue with their current therapy or be switched to home nocturnal HD for 6 months.[105] Blood pressure and anemia management was carried out for both groups using standardized, preset protocols. The patients' mean age was ~54 years, and mean time on dialysis was ~5.2 years. Approximately 63% of patients were male, 86% were white, 41% had diabetes, and 39% performed self-care or home conventional HD at baseline. In the intention-to-treat analysis, the primary outcome of left ventricular mass decreased by a mean of 13.8 (Standard deviation = 23) g in the nocturnal HD group and increased by 1.5 (SD = 24) g in the conventional HD group (mean difference = 15.3 g; 95% Confidence interval 1–29.6 g; $p = 0.04$). Using an observed cases approach (i.e., only those patients with baseline and 6-month cardiovascular magnetic resonance results [n = 35]), the between group difference was even more pronounced (mean difference = 19.7 g; 95% CI 1.9–37.4 g; $p = 0.03$). This difference persisted in sensitivity analyses with adjustment for baseline left ventricular mass and systolic and diastolic blood pressure. Antihypertensive use was reduced or discontinued in more patients on nocturnal than on conventional HD ($p < 0.001$). At the same time, nocturnal HD patients achieved reductions in blood pressure, whereas those on conventional HD sustained an increase (mean difference 14 mmHg; 95% CI 3 to 26 mmHg, $p = 0.01$).[105]

Compared to conventional HD, nocturnal HD was more effective at lowering serum phosphate, calcium-phosphate product, and parathyroid hormone levels.[105] However, there were no significant differences between groups in hemoglobin or mean erythropoiesis stimulating agent doses. Changes in the primary health-related quality of life measure were also not significantly different between groups, but improvements in selected kidney-specific quality of life domains were observed.[106]

Although the results of this randomized trial are promising, it is uncertain whether improvements in the surrogate outcome of left-ventricular mass translate into better long-term survival or other hard endpoints. One observational study suggested a decrease in the rate of hospitalizations because of cardiovascular causes in an unadjusted analysis. Bergman and colleagues retrospectively compared 32 patients on nocturnal HD to 42 conventional HD patients matched for age, sex, and vintage, but not

comorbidity.[107] After a mean follow-up of 26 ± 3 months, the cardiovascular hospitalization rate was reduced by 43% in those receiving nocturnal HD ($p < 0.05$), but there was no significant reduction in the total length of stay.

To date, there has been only one comparative study of survival with nocturnal HD. In this retrospective cohort study, patients receiving nocturnal HD in Toronto from 1994–2006 were compared to kidney transplant recipients from deceased and living donors registered in the USRDS database.[108] The 177 patients on nocturnal HD were matched to 533 living donor and 533 deceased donor transplant recipients on the basis of race, diabetes status, and duration of dialysis. Nocturnal HD patients had more comorbidities at baseline than the other two groups. There was no difference in the adjusted survival between nocturnal HD patients and deceased donor transplant recipients, whereas the survival of living donor transplant recipients was better than that of the other two groups. One limitation of this study is that the survival analysis was censored for change to conventional HD, potentially eliminating the most ill patients from the comparisons. In addition, no statistical power calculations were provided. Finally, the limitations of a cohort study where patients in both groups are systematically selected and data are collected retrospectively must be recognized. Notwithstanding these limitations, the findings from this observational study suggest that nocturnal HD patient survival may be closer to transplantation (the best currently known therapy for end-stage kidney disease), than to conventional HD.

Extended Hours Hemodialysis

The famous Tassin center in France has been performing extended hours HD for over 30 years. More recently, however, this regimen has been gaining popularity in Canada,[9] Europe,[13,109] Australia[10] and the United States.[11,12] This regimen has been seen to have certain advantages over frequent HD, particularly when performed in-center. Unlike short-daily HD, which may increase dialysis center workload and costs during the day, this regimen allows idle dialysis units to be used at night. It also opens up the option of more intensive HD to those patients who are unable to perform nocturnal HD at home, or who cannot come to the center 6 days per week for short-daily HD.

The data on long conventional HD are also limited to prepost observational studies, and the studies are not as numerous as with frequent HD. The largest experience is from Charra, who reports on 1348 patients treated with long conventional HD from 1968 to 2004.[8] While in the 1980s almost half of his patients dialyzed at home, now all but a few dialyze in-center. Approximately two-thirds dialyze thrice weekly for 7–8 hours during the daytime, whereas the remaining more stable patients dialyze at night. He reports apparently good blood pressure control with only 2%-5% of patients on antihypertensives. There are significant reductions in serum phosphate with just 30% requiring phosphate binders; however, the rate of vascular calcification was still high at >80% despite the intensive dialysis.[110] There have been improvements in nutritional status.[111] Charra also claims superior survival with long conventional HD, with 5-year survival rates of around 50% from 1995 onward.[8] However, it is difficult to interpret these results because there are no direct statistical comparisons between conventional and long dialysis in his study. Rather comparisons are made to USRDS data. Unlike dialysis patients in the United States, his patients are a highly selected group of prevalent patients (mean time on dialysis of 6.1 years). More than 80% of these patients have arteriovenous fistulae. Even if his case-mix has evolved to include patients with more comorbidities over the last decade, it is difficult to know whether his impressive results are due to an intensive "*HD schedule*" or to intensive "*physician care*." There are seven nephrologists who care for the 250 or so HD patients, and they create their own arteriovenous fistulae and even cannulate them each session if required.[8] Thus, for many reasons, it is difficult to ascribe causality to the impressive Tassin results.

Other studies of long conventional HD have demonstrated conflicting results. Powell and colleagues from the United Kingdom report a 10-year experience of 146 patients treated with long, overnight, thrice weekly HD; median follow-up was 2.2 years.[109] He compared 53 of these patients on long HD for at least 1 year to 53 control patients on conventional HD matched for age, sex, and diabetes status. The long HD patients had statistically significantly higher hemoglobin with a trend to reduced doses of erythropoiesis stimulating agents. While there was a trend to reduced phosphate binder requirements (number of pills = 5.9 [SD 3.6] vs. 4.8 [SD 2.6]; $p = 0.08$), there were no differences in serum phosphate. Unlike the Tassin report, there were no differences in blood pressure. Another study from Germany found no differences in 24-hour ambulatory blood pressure with extended hours compared to conventional HD, although a statistically significant decrease in left ventricular mass index was observed.[13] A recent Canadian study of 39 patients reported results similar to Charra.[9] Compared to the year before conversion to extended hours HD, there was a statistically significant reduction in serum phosphate, calcium phosphate product, and daily dose of phosphate binders after 1 year of the intensive therapy. There were no significant changes in anemia parameters, but antihypertensive use declined significantly. Significant improvements in quality of life were also observed.[9] These results need to be interpreted cautiously, however, because like the Ting study, they may also be affected by survivor bias. By 12 months, only 25 of the original 39 patients remained, yet data from all 39 patients were included in the baseline comparison measures. Finally, another U.S. prepost study confirmed reductions in serum phosphate but did not show any benefits on psychosocial assessments.[12]

In summary, the effects of long conventional HD on metabolic parameters are still unclear because the current studies are few and have serious methodological limitations. As with frequent HD, there are as yet no rigorous comparative studies of extended hours HD with conventional HD with respect to hard outcomes.

Potential Risks and Disadvantages

Because the published experience with frequent and extended hours HD is limited to <1000 patients, there are few to no data on the possible incremental risks of these therapies compared to conventional HD. However, several theoretical risks have been suggested.

Vascular Access Complications

Some have theorized that cannulating or hooking up to the vascular access twice as often with frequent HD may lead to increased access thrombosis, stenosis, or infections. In our systematic review of short-daily HD, we found that access dysfunction or permanent failures were significantly decreased in two eighths of studies, whereas there was a trend to increased arteriovenous fistulae dysfunction events requiring intervention in another two eighths of studies.[50]

With respect to nocturnal HD, Perl and colleagues reported significantly less central venous catheter changes required for poor blood flow during the period of nocturnal HD compared to conventional HD.[112] However, these results are potentially confounded because conventional HD requires a much higher blood flow than nocturnal HD (400 vs. 200 ml/min). Mahadevan and colleagues found significantly increased rates of arteriovenous fistula-associated bacteremia with nocturnal HD compared with short-daily and conventional HD (15 per 1000 days for nocturnal HD vs. 0 for the other groups).[113] There were no differences in vascular access events reported in the small randomized trial of nocturnal HD of 51 patients after 6 months of follow-up, but this study was underpowered to detect this outcome.[105]

In summary, the true rate of vascular access complications with nocturnal and daily HD is not known, but it is being more closely examined in two ongoing randomized trials and in the International Quotidian Dialysis Registry (see later text).

Blood Loss

HD results in small losses of blood with each treatment, and thus it stands to reason that increasing the frequency of dialysis may lead to increased blood loss. Surprisingly, this issue has been examined in only one study to date. Kooistra found that intravenous iron utilization significantly increased in 13 patients undergoing short-daily HD after 18 months of follow-up.[76]

Increased Exposure to Dialysate Water

Although dialysate water is disinfected and purified according to international standards, it is not 100% free of endotoxin, bacteria, and impurities. There is now a growing debate in the literature on whether exposure to these impurities leads to long-term complications of uremia and inflammation.[114,115] Patients undergoing all forms of frequent and extended hours HD are exposed to significantly more dialysate water than those undergoing conventional HD. Patients on conventional, long conventional, short-daily, and nocturnal HD are exposed to around 360, 430, 540, and 860 L per week of dialysate, respectively. Although it is uncertain that this increased exposure is harmful, some authors advocate the use of ultrapure dialysate filters for patients undergoing nocturnal HD, in addition to the usual reverse osmosis and deionization water purification systems.[116]

Water-Soluble Vitamin Deficiencies

Because extended hours and frequent HD increase solute clearances, it has been suggested that these therapies may lead to more water-soluble vitamin deficiencies. Vitamin C deficiency is currently being studied in an ongoing randomized trial of daily HD.[117]

Patient and Caregiver Burnout

This may be the main disadvantage of frequent and extended hours HD therapies. Conventional in-center HD itself is a demanding therapy, requiring patients who are generally not feeling well to come to the hospital on a set schedule, sit for many hours at time, and often endure considerable pain and discomfort. Patients take many medications daily, attend numerous other medical appointments, and are frequently admitted to the hospital. In-center short daily requires an even larger commitment from patients, who must come to the dialysis center 6 days per week and spend about 3 hours per day there. Arranging daily transportation poses one major barrier to this therapy for many patients, whereas others just tire of the daily treatments. In the systematic review, the median discontinuation rate for in-center short-daily HD was reported in five studies and was 41% after 3–24 months (range 0%-57%), censored for death and transplantation.[50]

For patients attending in-center extended hours conventional HD, arranging transportation can also be an issue given the hour of the day. In addition, patients may grow tired of sleeping at the dialysis unit away from their homes and families on a regular basis. Charra reports almost 100% compliance with extended hours HD over 5 to 20 years, whether done during the day or at night.[8] However, the experience of others is not so favorable. In Powell's study of long overnight thrice weekly HD, 33% switched back to conventional HD after a median follow-up of 2.2 years,[109] and in Bugeja's study of 39 patients, the discontinuation rate (censored for death, transplant, and loss to follow-up) was approximately 20% after 1.9 years.[9]

Frequent and extended hours therapies delivered at home pose a different set of challenges for patients. While patients do not need to come frequently to the in-center dialysis facility, they or their caregivers endure the burden of having to administer their own HD treatments. To set up the machine and start dialysis takes around 30–45 minutes, and another 15–30 minutes are required at the end of the treatment to disconnect and clean the machine. Patients must be organized to order supplies regularly and must accommodate home visits from the care team. Finally, patients must tolerate the intrusion of their HD therapy into their homes, similar to patients on peritoneal dialysis.[118] Many patients view their home as a place of refuge from their chronic illness and do not want to have the constant presence of the dialysis machine and equipment there. Despite being a highly selected group who are cognizant of the burden and are initially willing to undergo the therapy anyway, patients on home nocturnal HD can still suffer from burnout and fatigue, with a reported median discontinuation rate of 7% after 12–24 months (range 0%-15%).[50]

Catastrophic Events

Such events are thought of in the context of home HD and include sudden disconnection and exsanguination, air embolism, flooding of the home with dialysate, and difficulty to evacuate the home during a fire while on dialysis. Although all of these events are theoretically possible, careful patient selection, adequate training, use of proper equipment, and a focus on patient safety have rendered these events extremely rare. To date, the use of home HD has been restricted to a few select centers with highly experienced

and specialized care teams. However, it is possible that as home HD becomes more widespread, the rate of these complications may increase. The methods used to prevent these catastrophic events are discussed later.

Ongoing Studies

The theoretical physiological arguments in support of frequent HD are strong. Unfortunately, empiric evidence regarding the efficacy of these therapies is limited to mostly small observational studies with short follow-up and surrogate outcomes. Those that do examine hard clinical endpoints have methodological limitations. There is also a paucity of data on potential risks. Yet, aside from renal transplantation, no therapy to date has held such promise in improving outcomes for patients who are dialysis dependent.

In 2001, the National Institutes of Health (NIH) in the United States created a task force to determine the role of frequent HD.[119] A position paper was published, calling for 1) randomized trials of daily and nocturnal HD, and 2) creation of a North American Registry of frequent HD with the view to conducting rigorous, prospective, matched cohort studies. It was hoped that both of these endeavors would lead to a better understanding of frequent HD with respect to its efficacy, cost-effectiveness, potential risks, and barriers to implementation. In response to the Task Force, two projects were initiated: The Frequent Hemodialysis Network randomized trials[117] and the International Quotidian Dialysis Registry.[120] In addition, an Australian group has launched a multicenter trial of extended hours dialysis (www.clinicaltrials.gov, ID NCT00649298).

Frequent Hemodialysis Network Trials

Two NIH-sponsored randomized trials of frequent HD trials have been underway since 2005 in >20 centers in North America.[117] Recruitment is completed and results are expected by the end of 2010.

The first trial has randomized 245 patients to conventional thrice weekly HD to achieve an eKt/V of 1.2 per treatment as per NKF/KDOQI guidelines, versus short-daily six times weekly HD for 1.5 to 2.75 hours per session, to achieve a normalized eKt/V of 0.9 per treatment (Table 25-2). The weekly dialysis dose is expected to be about 50% greater in the short-daily versus conventional HD groups (std Kt/V ~3.8 vs. 2.5). All treatments are delivered in-center.

The second trial has randomized 87 patients to either conventional HD as above, or nocturnal HD delivered for at least 6 hours, 6 nights per week. The weekly clearance with nocturnal HD will be more than double that with conventional HD (std Kt/V ~5.6 vs. 2.5). Initially, the conventional HD treatments were delivered in-center, and the nocturnal HD was done at home. However, after a few patients were enrolled, the protocol was changed to ensure that both groups received their HD treatments at home to improve recruitment and avoid confounding by dialysis location.

The coprimary outcomes for both trials are 1) the composite of the 12-month change in left-ventricular mass index and death and 2) the composite of the 12-month change in the SF-36 Physical Health Composite score and death. There are several secondary outcomes, including blood pressure, hemoglobin, phosphate, depression scores, cognitive testing scores, physical functioning test scores, and hospitalizations, although the studies will not be powered to examine the latter. Adherence and modality switches are being monitored carefully. Data on potential risks are being collected, including vascular access complications, iron utilization, and vitamin C deficiency. Perception of burden on unpaid caregivers will also be assessed.

ACTIVE Dialysis Study

An Australian group is currently conducting a multicenter randomized trial of extended hours dialysis versus conventional HD (www.clinicaltrials.gov, ID NCT00649298). Subjects will receive at least 24 hours of dialysis per week, whereas controls will receive 12–18 hours per week. Initially, a pilot study will be conducted to determine the feasibility of recruitment with 40 patients, after which time a larger trial will be conducted. Multiple outcomes will be examined in the pilot study, including blood pressure, left-ventricular mass, hemoglobin, phosphate, and quality of life. Vascular access events and other safety outcomes will also be assessed. The pilot study is due to be completed in 2010, with final study results expected by 2014.

The International Quotidian Dialysis Registry

The Frequent Hemodialysis Network (FHN) and ACTIVE dialysis trials are not statistically powered to examine the potential survival benefits of frequent HD, and such trials are not practically feasible at this time.[121] A trial examining the effects of frequent HD on survival would require thousands of patients; recruitment of a few hundred patients for the FHN trials proved to be difficult. For this reason, large observational studies are likely the only means to

TABLE 25-2 Dialysis Prescriptions in the Frequent Hemodialysis Network Randomized Trials

	DAILY TRIAL		NOCTURNAL TRIAL	
Study Group	**Daily HD Arm**	**Conventional Arm**	**Nocturnal Arm**	**Conventional Arm**
Frequency	6 days/week	3 days/week	6 nights/week	3 days/week
Session Time	1.5-2.75 hr	2.5-5 hr	>6 hr	2.5-5 hr
Target Dose	eKt/V_n ≥0.9 per session*	spKt/V >1.2 per session	std Kt/V >4 per week	spKt/V >1.2 per session
Estimated Wkly std Kt/V	~3.8	~2.5	~5.6	~2.5
Treatment Location	In-center	In-center	Home	Home

*Corresponds to an spKt/V of ~1.1 per session.

evaluate whether frequent and extended hours HD lead to improved survival.

To this end, in 2003 efforts were begun to create the International Quotidian Dialysis Registry (IQDR). Endorsed by the NIH, the IQDR will provide detailed, longitudinal data on as many patients in the world as possible undergoing frequent and extended hours HD.[120] These data will then be used to conduct rigorous, observational, comparative cohort studies with hard endpoints. While the data management and infrastructure for this registry is housed in London, Ontario, the registry is a collaborative effort among multiple investigators from Canada, the United States, Australia, and more recently, Europe. The project is funded mainly through unrestricted grants from industry sponsors. Currently, the registry has over 2000 patients on frequent or extended hours HD therapies, and enrollment continues. Details on the purpose of the registry, its management structure, recruitment strategies, and planned studies can be found elsewhere.[11]

CURRENT INDICATIONS FOR FREQUENT HEMODIALYSIS

In absolute terms, delivery of frequent HD is more expensive than conventional HD, and its cost-effectiveness has not been studied directly. Consequently, frequent HD is presently funded for mainstream use in only a handful of centers throughout the world. Proponents of frequent HD continue to lobby funding bodies in North America to expand its use.[122,123] Until they are successful, however, in our opinion, there are certain medical conditions that may warrant the use of frequent HD as a *"salvage"* therapy. These include: 1) severe malnutrition not responsive to other measures, 2) Class III-IV congestive heart failure whereby ultrafiltration on conventional HD is limited by intradialytic hypotension or symptoms, and 3) refractory soft tissue calcification or calciphylaxis. In addition, although there are no controlled studies, case reports suggest that pregnancy outcomes for patients with ESRD may be improved with nocturnal HD.[104] If home HD is not possible or not desired by the pregnant patient, then we offer an in-center hybrid therapy of 5 hours, 5 to 6 days per week. Outside of these indications, the use of frequent HD is limited to study settings in most centers.

Although there are no established indications for long conventional HD, we believe this treatment may also be offered for "*salvage*" therapy as an alternative to frequent HD. Some centers with home conventional HD programs but without funding for frequent treatments have switched willing home HD patients to long conventional HD at night. This practice is thought to be relatively cost neutral (provided monitoring is not required—see later section) and offers patients the potential benefits of extended treatments. Dialyzing at night also allows patients to free up their day for other activities, such as employment, school, or recreation. Other centers have developed in-center long conventional programs at night for patients who are unable to dialyze at home. This is most common in the United States in for-profit HD units. However, in addition to increased nursing costs, this involves a change in the HD unit culture on the part of patients and staff and thus may not always be feasible.

LOGISTICAL ISSUES IN IMPLEMENTING FREQUENT OR EXTENDED HOURS HEMODIALYSIS PROGRAMS

Implementing frequent or extended hours HD programs requires adequate medical, nursing, and biomedical expertise; appropriate funding; and a suitable infrastructure. Perhaps the most important feature of a successful program, however, is modification of the HD unit culture,[124] such that patients are willing to try the new modalities, and front-line staff are willing to modify their work schedules and duties in order to offer them. In this section, we review some of the practical aspects involved in delivering these intensive HD therapies.

In-Center Daily Hemodialysis

As discussed previously, the schedule of conventional HD emerged because it was thought that three times weekly HD was likely adequate, and three 4–5 hour shifts fit conveniently into a 15-hour workday. A three times per week schedule allows six patients to be dialyzed on a single machine each week. With short-daily HD, the session times are shorter (1.5–2.5 hours), and thus one might propose to fit two short-daily sessions into one conventional HD time slot. However, because the turnover takes at least 45 minutes, and HD units also have to deal with the reality that some patients come late, such a solution is not usually feasible. For dialysis facilities where most patients are treated with thrice weekly HD in 4–5 hour time slots, accommodating short daily dialysis patients means reducing the number of patients dialyzed each week. To accommodate these patients, the unit either has to stay open longer, or extra HD stations (with concomitant capital and labor costs) must be created. This results in increased costs for the HD unit.

Aside from potentially increased costs for the HD unit, the workload for the nursing staff is more with short-daily HD, increasing the likelihood of burnout and difficulties acquiring staff. With conventional HD, one nurse can easily manage three stations at a time, provided the on-off timings are staggered. He or she would thus be responsible for putting on and taking off six patients during an 8 hour shift. With shorter session times, however, there is a much higher turnover of patients, and he or she would be responsible for 10–12 patients during an 8 hour shift.

To overcome these difficulties, HD units offering in-center daily HD have developed unique solutions in keeping with the unit's individual needs. If the HD unit is not at maximal capacity, accommodating a few patients on short-daily HD may not pose a problem. If the unit is full, then one solution is to fit two daily patients into a single conventional HD time slot just in the morning and follow the morning shift with a patient who is receiving conventional HD for $\leq$3 hours/session. This keeps the evening shift on time and does not increase the overtime labor costs for the unit. At the same time, a single nurse does not become overburdened with too many turnovers. This is the solution we have used successfully at our unit. Another strategy that has been used is to give patients approximate rather than fixed appointment times (N Levin, personal communication). When they arrive for their session, they can then be accommodated at whatever

HD station is free. This *"running schedule"* allows flexibility for both staff and patients, but one disadvantage is that the HD prescription cannot be programmed into the machine ahead of time. No matter what solution is decided upon, flexibility and open-mindedness on the part of nurses, staff, physicians, administrators, and patients is essential.

In-Center Extended Hours Overnight Hemodialysis

Many units, particularly free-standing units in the United States, see this modality as being very easy to implement because no extra capital or infrastructure is required. However, this modality requires an entire paradigm shift in the HD unit. Nursing staff and technicians are required to work night-shifts, physicians must be on-call and round during the night, and patients are required to sleep at the HD unit 3 nights per week. Given that not having to work nights is one of the main factors attracting nurses to HD, it may be difficult to staff overnight HD in localities where there are nursing shortages. Other logistical concerns include arranging for patient transportation at night for those who are not able to drive themselves. Despite these challenges, this modality has been gaining popularity. The two largest dialysis providers in the United States reported treating more than 1600 patients with thrice weekly in-center overnight dialysis in March 2009 (in press).

Home Frequent or Long Conventional Hemodialysis

Although in-center frequent or extended hours HD offers an attractive option for many patients, not all may accept the requirement for daily transportation or sleeping at the HD unit, but they would still like to enjoy the potential benefits of intensive HD. Such patients may choose to dialyze at home. One advantage of home HD is that it allows patients the flexibility to choose their own schedules and the autonomy to become more involved in their own care. Implementation of a home HD program requires the creation of a unique and adequate infrastructure, no matter what the frequency of therapy. The complete details of how to set up a home HD program are beyond the scope of this chapter, but a synopsis is provided below. This description and these recommendations are based on more than 225 patient-years experience of delivering home and home frequent hemodialysis at the University of Western Ontario since 1998, under the direction of Dr. Robert Lindsey.

Personnel

Specialized and competent personnel are critical to the success of any home hemodialysis or peritoneal dialysis program. Home hemodialysis nurses with the expertise to teach patients and their families and ability to problem solve are required. A head nurse with strong leadership skills should serve as a resource for other nurses, anticipate problems, and provide continuity of care. These nurses are responsible for initial assessments and patient training. This usually occurs one-to-one, but two experienced nurses can simultaneously train three patients. Once patients are established on home HD, the nurses provide telephone follow-up, arrange blood work and clinic visits, troubleshoot problems, conduct periodic home visits, and serve as a liaison between the patient and the physician. They are also on call after-hours. Ratios will vary from center to center, but at our center, we have one nurse for every 20 patients on home HD. A secretary manages the day-to-day clerical work.

Biomedical engineers and technicians are needed to oversee the plumbing installation, routinely test the patient's water quality, and maintain and troubleshoot problems with the patients' HD machines. We have one biomedical engineer for every 25 patients, and they are on call for 12 hours/day, 7 days/week.

Facility

The home HD unit should have training rooms that are plumbed for HD, rooms for clinic assessments, a conference room for multidisciplinary team meetings, storage space, and offices for the secretary, head nurse, and physician.

If desired, a remote monitoring station can be set up at the home HD unit. Monitoring is only needed for night-time HD, but some centers choose not to monitor at all.[105,124] A telephone modem transmits machine data every 20 seconds to the central computer, where a person (the monitor) watches for machine alarms. If the patient does not wake up to the machine alarm, the monitor phones the patient. If there is no answer, the monitor calls 911 and sends emergency services to the patient's home. The value of remote monitoring is highly debated. Theoretically, monitoring improves patient safety and relieves patient anxiety. The latter should not be underestimated given that fear of catastrophic events is a major barrier to patients choosing home HD.[125] However, it should be remembered that these systems transmit machine data, not patient or wet/spill alarm data, and if a catastrophic event did occur, by the time emergency personnel arrived, it might be too late to be effectual. Moreover, because of the high load of information, equipment breakdowns are not infrequent. In the London study of 12 nocturnal HD patients, there were ~5300 alarms in over 4000 patient nights.[126] Approximately 350 calls were made to the patient's home, and none were made to 911. Most of the alarms were due to arterial or venous pressure alarms, and there were no catastrophic events. Because most of the events occurred during the first month, we now require monitoring during only the first 3 months of nocturnal HD. We continue monitoring only for those patients who request it to alleviate their anxiety or who have ongoing concerns. We believe that careful patient selection and proper training are more important than continued monitoring (see later text).

Equipment, Water, and Supplies

A number of specific features have been described for the "ideal" home HD machine (Table 25-3).[127] There are several HD machines specifically marketed for home HD, each with at least some of these features, but, unfortunately, no company has been able to incorporate all of them. The requirement for high technology features needs to be balanced with user-friendliness. The more "bells and whistles" that a machine has (e.g., blood volume monitoring, on-line clearance monitoring), the more complicated it may be to use and the more prone it may be to breakdown. We prefer a machine that can deliver a range of dialysis doses for conventional, extended-hours, and frequent

TABLE 25-3 Characteristics of the Ideal Home HD Machine

- Easy to learn
- Compact and aesthetically pleasing
- Portable, suitable for travel
- Quiet
- Minimal time to set up and connect
- Minimal time to disconnect and clean
- Minimal maintenance required
- Inexpensive
- Large screen with good contrast and large fonts
- Controls accessible from seated or supine position
- Can deliver a range of doses, for conventional, short-daily, nocturnal, and extended hours HD
- Range of blood flows possible (150-450 ml/min)
- Interchangeable dual pump module to allow for single needle HD
- Range of dialysate flows possible (200-800 ml/min)
- Compatible with most dialyzers
- Able to provide ultrapure water
- No need for anticoagulation
- Ability to transmit data to monitoring station through Internet

HD, and is compact and quiet with large screen fonts and controls accessible from a chair or supine position. In addition to the machines, programs need to choose a water treatment system to be installed in the patients' homes, either reverse osmosis (RO) or deionization (DI), as detailed elsewhere.[128] We suggest additionally adding an extra filter on the dialysis machine circuit at the point just before the dialysate reaches the dialyzer, in order to provide as close to ultrapure water as possible. This filter needs to be changed every 3 months.

There should be provisions made for delivery of supplies to the patient on a frequent basis, including dialyzers, blood lines, water filters, concentrate, gauze, masks, blood test collection tubes, and so forth. Usually this job is subcontracted out to a medical supply delivery company. Finally, all patients should ideally have a centrifuge to allow them to spin their blood samples before they send or take them to the laboratory.

Patient Selection

Patients who wish to undergo home HD should take part a detailed assessment of their medical history and social situation. Similar to peritoneal dialysis, there are no validated criteria in selecting patients for home HD. In our opinion, the most important criterion for successful home HD is a motivated and willing patient. Patient perceived barriers to home HD include lack of confidence in self-cannulation, comfort with their current therapy, not wanting to overburden caregivers, and fear of catastrophic events.[125] Many of these barriers can potentially be overcome with patient and caregiver education. However, there are several relative medical and social barriers that may preclude home HD, and these should be evaluated before pursuing home HD as an option (Table 25-4). Some of the barriers may potentially be overcome if patients have a suitable caregiver.

If patients are deemed suitable for home HD, they must then undergo an evaluation of their home (see Table 25-4). In many cases, it may be more efficient to complete the home and patient assessments simultaneously. If the patient lives in a rental property, it may be necessary to seek written permission from the landlord for home HD. There must be ample space to accommodate the machine, water system, and supplies, and appropriate access to the room where the patient will be dialyzing. The home must be clean, have a potable water source with adequate water pressure, and have a proper electrical supply. Sometimes renovations will need to be done to meet all of these requirements; whether these must be paid for by the patient or are covered by the program varies between centers.

TABLE 25-4 Contraindications and Barriers to Home HD: Patient Selection

Absolute Contraindications
- Planned transplant within the next 6–12 months
- Planned move out of region in the next 6–12 months
- Noncompliant to medical care
- Extremely poor hygiene
- Uncontrolled seizures
- Significant hemodynamic instability on HD requiring frequent nursing intervention
- Extremely poor general health with life expectancy <1 year
- Patient does not want home HD

Medical Barriers—can be potentially overcome if there is a caregiver who can help with and administer the dialysis treatment
- Decreased hearing/deafness
- Decreased vision/blindness
- Decreased manual dexterity
- Decreased strength to lift supplies/poor mobility

Cognitive Barriers—can be potentially overcome if there is a caregiver who can help with and administer the dialysis treatment
- Any impairment that makes patient unable to learn home HD procedures, for example:
  - — Significant anxiety
  - — Dementia
  - — Significant psychiatric disorder
  - — Significant learning disability
- Aphasia/dysphasia that impairs communication with the healthcare team

Social Barriers—can potentially be overcome if circumstances change
- Moving out of region in the next 12 months
- Patient is primary caregiver for another individual and is burnt out
- Language barrier that interferes with adequate training or telephone communication
- Lives a significant distance from the training center and cannot afford lodging during training period
- Cannot afford to take time off employment to train
- Employment interferes with performing home HD regularly

Residential Barriers—can potentially be overcome if circumstances change
- Patient is homeless
- Patient is living in rental property, and landlord did not grant permission
- Unsuitable access to room where home HD will be performed, impairing delivery of equipment and supplies
- Small living space that cannot accommodate machine/supplies
- Water supply inadequate, for example, nonpotable water, poor water flow, low water supply
- Inadequate electricity
- No private phone line to communicate with home HD center
- Cost for renovations prohibitive to residence/plumbing/electrical supply
- Patient cannot afford extra utility costs, for example, water, electricity, garbage disposal

Training

Patients require individualized training by highly skilled nurses.[129] The teaching style, language level, and time spent must be tailored to meet the patient's needs. For most patients, adequate training takes about 4 weeks if trained for 5 days/week and 6 weeks if trained for 3 days/week; for those who have been performing some form of self-care HD, this time may be reduced. The training manuals and

educational materials should be written at a grade 6 level or less, in order that the majority of patients may understand them. Specifically designed manuals with large font, in languages other than English, and with extra pictures may be required for some patients. All patients are taught how to set up and operate the machine, cannulate their arteriovenous access or connect to their tunnelled catheters, set ultrafiltration targets, administer intravenous medications, deal with common alarms, disconnect themselves, and clean the machine. In addition, they learn how to deal with common emergencies such as hypotension, bleeding, accidental disconnection, and how to evacuate in case of a fire. Once the training is completed, the nurses make periodic home visits to the patients' homes and observe them dialyzing to ensure that proper techniques are being followed. We recommend that before a center embarks on their own home HD program that they send one or two nurses to an experienced center to learn the principles and nuances involved in training patients safely.

Vascular Access and Safety Considerations

Some centers send patients home with tunneled catheters only, whereas others use arteriovenous fistulae only. We have successfully trained patients with all types of HD accesses, and each has its advantages and disadvantages, similar to those for patients on in-center HD. For arteriovenous fistulae, we recommend cannulation using the buttonhole technique.[130] With this technique, the same cannulation site is used repeatedly for each treatment, such that within a few weeks, an epithelialized tract is formed, making subsequent cannulations much easier. This is in contrast to the "rope-ladder" technique where the cannulation sites are rotated with each treatment. Some have noted an increase in infections with the buttonhole compared to the rope-ladder technique, but these may be prevented with the use of antibacterial cream over the buttonhole sites (G Nesrallah, personal communication). This requires further study.

All patients are taught how to tape the arteriovenous fistula needles in place so they are secure. If patients are undergoing HD while sleeping, the security of needles is particularly important to avoid accidental disconnection. We place clear sticky dressing tape over the needle and tubing; others tape at the site of insertion using the Chevron method. We tape an enuresis alarm over the needle and place moisture sensors on the floor to detect any bleeding from disconnection. The moisture sensor has the added advantage of detecting dialysate leaks. In addition, we use only single needle HD and slow blood flows around 200–250 ml/min for patients on nocturnal HD; a dual pump alternates flow forward and backward. This is done to reduce the likelihood of exsanguination in case of accidental disconnection. With a two-needle HD, if the venous needle falls out, blood will continue to be pumped from the arterial needle until the machine senses the drop in venous pressure and stops the blood pump. This may take a few seconds, during which time a significant amount of blood may be lost. If the needle falls out with single-needle HD, the patient bleeds from the cannulation site only, at a slower flow rate.

There are also several safety considerations when connecting to a tunneled HD catheter. A special connector is used to ensure that the blood lines do not disconnect from the catheter, and moisture sensors are placed on the floor. In addition, it is imperative that the proper closed system and needleless connectors be used between the HD catheter and the blood lines to avoid air embolism.

ECONOMIC CONSIDERATIONS

Dialysis Delivery Costs

In-Center Frequent and Extended Hours Hemodialysis

In-center frequent HD increases dialysis delivery costs because of double the use of disposables; such as dialyzers, tubing sets, dialysate, and other supplies. Dialysate costs are also more. Labor costs are also likely increased because of more patient hook-ups and take-offs. As centers become more experienced and enroll more patients, economies of scale, new schedules, and better work flow could allow more efficient delivery of these new therapies, and identification of cost savings. If frequent HD increases patient stability, then nurse-to-patient ratios may be reduced, potentially lowering labor costs.

In-center daily dialysis disrupts the conventional schedule of thrice weekly dialysis. In a dialysis facility running three shifts 6 days a week, one dialysis machine accommodates six patients each week. If that same machine is used for short daily dialysis, it will accommodate just five patients/week, thus reducing the unit's efficiency. If a facility with a growing population of frequent HD patients wishes to maintain its volume, additional dialysis machines and space would be needed. For example, 24 patients could be dialyzed with four machines on conventional HD, but if these same 24 patients all chose short-daily HD, then an extra machine and station would be required to dialyze the last four patients.

In-center extended hours HD doubles dialysis time and requires nursing and medical supervision during the nights. This increases operating expenses because of having to keep the unit open at night (e.g., electricity, heating/air conditioning), expanded dialysate utilization, and compounded labor costs. If nurse-to-patient ratios can be reduced, there may be some cost savings, but this may be counterbalanced by the requirement for nighttime premium pay in some places.

Finally, other costs that must be considered for in-center frequent and extended hours HD are those usually borne by the patient, such as transportation.

Home Frequent Hemodialysis

In addition to increased disposables, the costs of home frequent HD relate to setting up the individual patient to dialyze in his or her home. This includes purchase of the HD machine and water purification system and installation costs. Who pays for these costs varies from center to center. Modifications to the plumbing are usually covered by the dialysis provider, but patients are usually responsible for any carpentry renovations (if required), such as changing the size of or improving access to the room where the HD will be performed. The machine and water system can be reused for someone else if the patient discontinues home HD, but the installation costs are nonrecoverable. At our center, we have determined that a patient must remain on home HD for an average of 12–14 months for the costs of

TABLE 25-5 Typical Prescription Parameters for Conventional, Frequent, and Extended Hours HD

	CONVENTIONAL HD	DAILY HD	NOCTURNAL HD	EXTENDED HOURS HD
Time (hours)	2.5-5	1.5-3	6-8	6-8
Frequency	3 days/wk	5-7 days/wk	5-7 nights/wk	3-4 nights/wk
Qb (ml/min)	350-450	350-400	150-250	150-250
Qd (ml/min)	500	750-800	300	300
Needling of AVF	Double	Double	Single	Single
Kd (ml/min)	250	300	150	150-200
spKt/V	1.3	1-1.1	1.4-1.6	1.6
Wkly std Kt/V	2.1	3-3.5	4-5.5	2.5-3.5

AVF, arteriovenous fistula; *Qb*, blood flow rate; *Qd*, dialysate flow rate.

capital and installation to be offset by savings on labor costs as a result of not dialyzing in-center.

Home HD training centers require expenditures to develop and maintain the home HD infrastructure. Biomedical technicians, nurses for training and ongoing troubleshooting, dieticians, and social workers are critical components. These costs are usually offset once a "*critical mass*" of home patients has been enrolled, as personnel time is used more efficiently, and labour costs of having to dialysis these patients in center are reduced. While some centers do not remotely monitor their patients who perform night-time HD,[105,124] others pay for remote monitoring if required by law or desired by patients. Costs for a remote monitoring station can be shared by several home HD programs within a given region, potentially reducing costs. Finally, the patient should be aware of increased electricity, water, and garbage disposal costs that may result from performing home HD.

Cost-Effectiveness

From a dialysis provider's perspective, it is the dialysis delivery costs that matter. However, from a societal or even a healthcare budget perspective, cost-benefit analyses are more important. If frequent and extended hours HD result in improved health, the increased delivery costs may be offset by lower costs of medications, hospitalizations, medical procedures, and government disability payouts. Even if the cost-benefit analyses are not favorable (i.e., overall there is not a cost savings when all costs are considered from the societal perspective), the therapies may still be valued to be cost-effective if they result in improvements in survival and/or quality adjusted life years. It is uncertain how high a cost-effectiveness ratio for which society is willing to pay,[131] but accurate data regarding the costs of delivery of these modalities and their efficacy are required before these assessments can be made.

There are no published empirical cost-analysis studies on in-center frequent or extended hours HD. However, one study that modeled the cost-effectiveness of daily HD concluded that for in-center frequent HD to be cost neutral, the per session HD costs would have to be reduced by approximately 32%-43%. Otherwise, cost-effectiveness ratios ranged from $75,000 to $125,000 per quality adjusted life-year saved, relative to conventional HD.[132] Conversely, based on observational empirical data, it has been suggested that home frequent HD is a dominant therapy, resulting in improved health with an overall cost savings to the healthcare system.[122,133,134] However, given the as yet unproven efficacy of frequent HD, further studies are required to conclusively confirm this statement. Until there is more evidence on the true efficacy of these modalities, their true cost-effectiveness and cost-utility will be unknown.

THE HEMODIALYSIS PRESCRIPTION

Typical prescriptions for short-daily, nocturnal, and long conventional HD are provided in Table 25-5. Considerations in determining the individual HD prescription for intensive HD therapies include clearance requirements, electrolyte changes, calcium and phosphate balance, and ultrafiltration goals.

Urea Clearance

Although urea clearance may not be the single measure of dialysis adequacy,[135] it remains one major criterion. For the frequent and extended hours HD therapies, urea clearance may be expressed as weekly standard Kt/V, a concept originally proposed by Gotch (Figure 25-4).[136] Std Kt/V can be calculated from the single pool Kt/V using a simplified equation developed by Leypoldt,[137] and website calculators are available for this purpose.[138] For conventional HD with a per treatment single pool Kt/V of 1.2, the weekly std Kt/V would be ~2.0. It is important to note the std Kt/V has not yet been validated against patient outcomes, but to date it is the most widely used measure of weekly urea clearance.

For short-daily HD, maximum blood flows, high surface area dialyzers, and higher dialysate flow rates of 750–800 ml/min are suggested to maximize weekly small solute clearance. Short-daily HD delivered in this way (with conventional HD machines, not NxStage System One) for ~2 hours, 6 days per week results in a single pool Kt/V of only ~0.9 (PRU 57%), yet the weekly std Kt/V is approximately 50% higher than with conventional HD (~3.0).[39] It is important to note, however, that patients will not always be 100% compliant. If patients on short-daily HD miss some sessions or shorten treatment times, it is possible that their weekly urea clearance may drop to below what they would be achieving if they were compliant with conventional three times per week HD. To ensure this does not go unrecognized, we recommend carefully reviewing patients' treatment run sheets for frequency and time regularly and measuring the pre- and posturea at least monthly. The std Kt/V calculator can then be used to estimate the actual weekly clearance

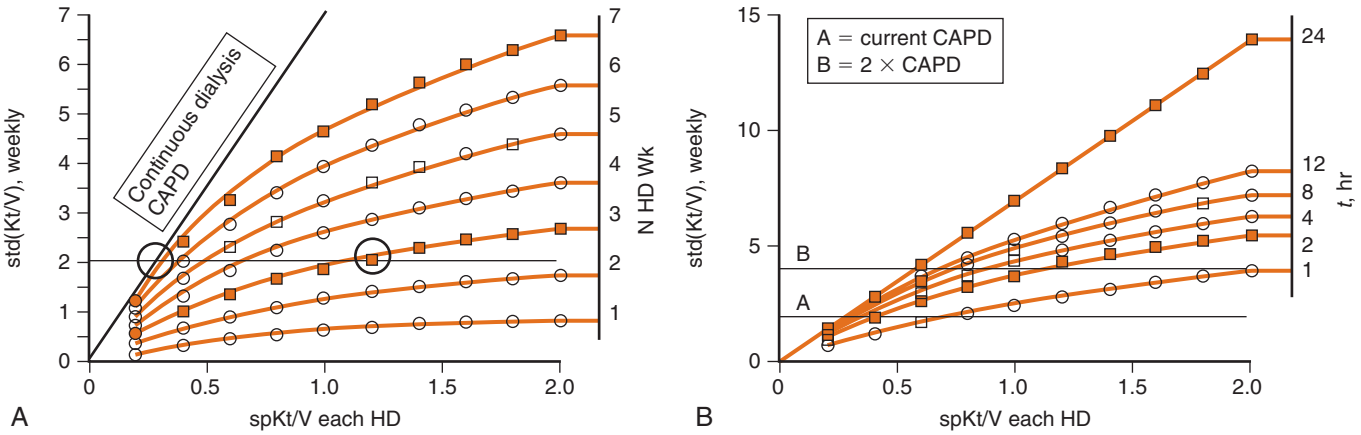


FIGURE 25-4 The relationship between weekly standard Kt/V (stdKt/V) and per dialysis single pool Kt/V (spKt/V). **(A)** shows the effect of varying frequency on stdKt/V with dialysis session time held constant at 3.5 hours each dialysis. **(B)** shows the effect of varying treatment time on stdKt/V with a dialysis frequency of 7 days per week. Note that stdKt/V is dependent on session time even with daily intermittent hemodialysis. (Data from F.A. Gotch, The current place of urea kinetic modelling with respect to different dialysis modalities, Nephrol. Dial. Transplant. 13 (Suppl. 6) (1998) 10–14.)

received.[138] If patients are missing sessions regularly, then treatment time may need to be increased for the sessions they do attend in order to maintain adequate clearance. In this situation, the care team must consider whether the patient is really achieving the potential benefits of short-daily HD or whether he or she should switch back to conventional HD.

With longer nocturnal HD, clearances of small and middle molecules are increased even at lower blood flow (150–250 ml/min) and dialysate flow rates (250–400 ml/min). Lower blood flow rates decrease blood loss in case of accidental leakage, whereas lower dialysate flow rates decrease water costs. Thus for nocturnal HD, lower blood and dialysate flow rates are preferred. We use a dialysate flow rate of 300 ml/min and blood flow rate of 200 ml/min. Under these conditions, patients are still able to achieve a spKt/V of around 1.6 (PRU 67%) per 7-hour treatment, providing a weekly std Kt/V of ~4.6 delivered 5 nights per week.[39] Even if patients miss treatments dialyzing only 4 nights per week and shorten time down to 5 hours, the std Kt/V will still be >2.7, provided the single session spKt/V is >1.2.[138] For this reason, the measurement of urea clearance is not so important for patients dialyzing 4–6 nights per week, but, of course, treatment run sheets should still be reviewed regularly for compliance with the therapy.

For patients dialyzing an average of 3 or 3.5 nights per week, the same does not apply. With long conventional HD, the weekly std Kt/V may be similar to that of conventional HD if low blood and dialysate flow rates are used. Just as for conventional HD, we recommend monitoring for underdialysis by monthly review of the treatment run sheets for time and frequency and measurement of spKt/V to ensure that the minimum target of 1.2 is being met.

It should be mentioned that for patients who dialyze at home and are savvy enough to falsify the treatment run sheets, increases in predialysis urea and creatinine from month to month may be a clue to noncompliance.

Dialysate Composition

The concentrations of potassium, bicarbonate, calcium, and phosphate may require adjustment when patients are switched from conventional to either frequent or extended hours HD. We suggest frequent monitoring of these serum electrolytes initially, followed by monthly blood tests once patients are stabilized on the therapy.

With nocturnal HD, patients can lose considerable amounts of calcium in the dialysate, resulting in negative calcium balance and secondary hyperparathyroidism.[139] This problem is usually compounded when increased phosphate removal on nocturnal HD prompts discontinuation or reduced use of calcium-based phosphate binders. We therefore treat patients on frequent nocturnal HD with a dialysate calcium concentration of 1.5 mmol/L (3 mEq/L). The dialysate calcium concentration should be increased further and/or oral calcium carbonate added between meals as necessary to maintain the post-dialysis serum corrected calcium in the normal range. Concerns have been raised that use of higher calcium dialysate in the setting of nocturnal HD may increase vascular calcification and mortality,[140] but this hypothesis has not yet been tested.

Hypophosphatemia may be a life-threatening complication of nocturnal HD, so serum phosphate must be monitored carefully. If the postdialysis serum phosphate is below the normal range, the patient's binders should be discontinued and the dietary phosphorus increased. Some have reported that they actually need to add phosphate to the dialysate bath to maintain a normal serum phosphate, but this has not been our experience. If required, ~0.07 to 0.14 mmol can be added to the dialysate before each treatment (65 to 130 ml of Fleet Phospho-Soda, 1.06 mmol/L). With short-daily and extended hours HD, negative calcium and phosphate balance are not usually significant issues, but we suggest monthly monitoring anyway.

For all intensive HD therapies, dialysate K and HCO_3^- should be adjusted to maintain normal predialysis serum concentrations of these electrolytes.

Target Dry Weight

Because of increased ultrafiltration ability, patients on extended hours and frequent HD may achieve a significant reduction in their target dry weights and possibly normal

blood pressure without the use of antihypertensives. For patients dialyzing in-center, we initially recommend assessing the dry weight and need for antihypertensives once or even twice weekly. It is unclear what is the best time to measure blood pressure to make treatment decisions, even in conventional HD patients.[141,142] We use an average of the predialysis, intradialysis, and postdialysis blood pressure.[143] As the blood pressure normalizes, we first discontinue the patient's antihypertensives. If the blood pressure then increases, we aim to reduce their target weight. Some patients increase their nutritional intake, resulting in increased lean body mass, and thus frequent assessments of *"dry weight"* may be required. Once the patient stabilizes on the therapy, the frequency of assessments can be reduced.

Patients who dialyze at home should be taught how to adjust their target weights based on their blood pressure, and followed closely by telephone. We initially schedule frequent follow-up visits and then reduce clinic visits to once or bimonthly once patients are stabilized.

FREQUENT HEMODIALYSIS IN CHILDREN

Intensive HD regimens have been used infrequently in children,[144] but reports of its use are increasing.[145,146] Many of the same considerations apply as for adults, but maintaining normal calcium balance and vitamin levels are likely more important in order to sustain normal growth and bone function.[147] In addition, issues of well-being and burnout of caregivers require special consideration in this population.

NXSTAGE SYSTEM ONE

The NxStage System One is becoming increasingly popular in many centers in the United States.[15] This HD machine has the advantages of being compact, easy to learn how to operate, with short setup and disconnect times (<20 minutes).[148] The system uses a dialysate generation system called PureFlow, or patients can use prepackaged bags of dialysate, allowing travel. Patients can perform the treatment nightly while they sleep or during the day for 2–3 hours per session. Costs of this therapy have not been published, but it is likely cheaper than in-center or even home conventional HD. Because of these features, this machine has the potential to greatly expand the pool of patients who are willing and able to do home HD. This is obviously appealing, given the rising cost of in-center HD. Improvements in blood pressure and interdialytic weight gain have been reported,[149] as have improvements in depressive symptoms and time to recovery after a dialysis treatment.[150] One of the main disadvantages, however, is that, despite being a daily therapy, this system does not deliver weekly small solute clearances higher than those of conventional HD.[149] This is because dialysate flow rates are limited to ~15 L per treatment with the NxStage system. Thus, although an important advance in HD technology, this therapy is not the same as other frequent HD therapies and should be considered in its own context.

FUTURE DIRECTIONS

The use of frequent and extended hours HD has expanded considerably in the last decade, and this growth is expected to continue. However, before this therapy can become "mainstream," there is much work that needs to be done. More evidence is required regarding the potential risks of these therapies and their efficacy in improving hard outcomes. It is also not clear whether these therapies are cost-effective, hindering their acceptance by funding bodies. The absence of adequate reimbursement mechanisms is the major impediment to widespread use of frequent HD in most countries. Other barriers include lack of physician comfort and expertise, unsuitable infrastructure or culture of HD units, and poor patient acceptance of the therapies. Patient selection and eligibility criteria must be clarified to ensure that those offered the therapies have the best chances of remaining on these modalities long-term. Finally, improvements in technologies are needed to decrease the amount of time involved in setting up and connecting to the machine, both for in-center and home frequent HD. Many are working to resolve these issues so that frequent and extended hours HD may become viable options for patients with ESRD in the majority of centers around the world.

A full list of references are available at www.expertconsult.com.

Chapter 26

PERITONEAL PHYSIOLOGY

Olof Heimbürger, M.D., PhD

In patients with chronic renal failure, waste products, which normally are excreted in the urine, accumulate in the blood resulting in uremic intoxication, and the obvious goal of dialysis treatment is to remove *"uremic toxins"* (including water) from the patient. Peritoneal dialysis (PD) uses dialysis fluid infused into the peritoneal cavity and a system of biological membranes—the peritoneal barrier—for this purpose. Whereas the artificial hemodialysis membrane has well-characterized, reproducible, solute and fluid transport characteristics, the peritoneum is not really a membrane but rather a complex structure of living tissues with different transport characteristics, which, furthermore, will differ between patients, a fact that will affect the fluid and solute transport kinetics of PD and dialysis efficiency in PD patients. In addition, the transport characteristics of the peritoneal membrane may not be constant in an individual patient but may be altered with time because of effects of the dialysis procedure or the dialysis fluids, in response to various physiological reactions or pharmacological effects of different drugs.

PERITONEAL ANATOMY

The peritoneal cavity is the largest serosal cavity in the body with a surface area of approximately 1 to 2 m^2. Although the peritoneal area is commonly suggested to be similar to the body surface area, recent studies suggest that the anatomical surface area of the peritoneum may be only about 50% of the body surface area in adults.[1–3] Peritoneum etymologically means *"wrapped tightly around,"* which is a good description of the arrangement of this serous membrane that consists of two parts: the parietal peritoneum that covers the abdominal wall, and the diaphragm and the visceral peritoneum that covers the intra abdominal viscera.[4] The parietal peritoneum represents a smaller portion (approximately 10% to 20%) of the total peritoneal surface area[1,2] and receives its blood supply from the vasculature of the abdominal wall. The visceral peritoneum represents the larger part (approximately 80% to 90%) of the total peritoneal surface area[2] and receives its blood supply through the mesenteric vessels. However, it should be pointed out that it is the functional peritoneal

surface area that is important not the anatomical surface area.[5] The functional area will be related to the surface area of the capillaries in the peritoneal interstitium, the capillary density, and the spatial arrangement of these capillaries.[3,5] In addition, the peritoneal cavity is only a potential space under normal conditions and the functional contact area between the peritoneum and the dialysis fluid in the peritoneal cavity during PD will be lower than the anatomical area.[6] In particular, functional area of the visceral peritoneum is reduced because of the incomplete contact and poor mixing in small fluid compartments within pockets of the visceral peritoneum. In mice, less than half of the peritoneal surface is in contact with a large volume of solution in the peritoneal cavity, but the contact area could be improved by shaking of the animal, and, particularly, by adding dioctyl sodium sulfosuccinate (a surface-tension lowering agent).[6]

HISTOLOGY

Mesothelium

The surface of the peritoneal cavity is lined by a single layer of mesothelial cells (fixed to a continuous basement membrane) that under normal physiological conditions are covered with a thin (5 μm) film of peritoneal fluid that is kept in place by numerous microvilli.[4] The microvilli and the peritoneal fluid have a lubricating function to prevent formation of adhesions and to allow the free movement of the visceral organs during respiration, peristalsis, and body movement.[4] The peritoneal fluid contains protein, electrolytes, and cells (mainly macrophages, lymphocytes, and desquamated mesothelial cells), and has a high content of phospholipids that are secreted in from the mesothelium by the formation of lamellar bodies, similar to the production of surfactant from type II pneumocytes.[7]

The mesothelial cells may modulate the peritoneal microcirculation by secretion of vasodilators like PGE_2 and nitric oxide and vasoconstrictors, such as endothelin,[8] and, furthermore, the mesothelial cells have an important role in the initiation of the local immune response regulating leukocyte infiltration through the secretion of chemokines and expression of adhesion molecules.[9,10] Mesothelial cells have a capacity to produce tissue plasminogen activator (tPA), and the mesothelium normally expresses high fibrinolytic activity.[8,11] However, the mesothelium also have antifibrinolytic capacity by synthesis of fibrinolytic inhibitors like plasminogen activator inhibitor 1 (PAI-1) and PAI-2, and the balance between the synthesis of fibrinolytic and agents in mesothelial cells will determine their capacity to promote fibrin degradation. Under normal conditions the fibrinolytic activity strongly dominates, but the balance may change completely during inflammation when the antifibrinolytic activity of the mesothelium will dominate, and furthermore, the mesothelium may also exhibit procoagulant activity with expression of tissue factor (which is markedly upregulated in mesothelial cells during inflammation).[8] Thus the mesothelium plays an important role in regulation of the balance between fibrinolytic and procoagulant activity in the peritoneal cavity.

The underlying basement membrane is a very thin laminar network containing collagen type IV, proteoglycans, and glycoproteins such as laminin, and allows macrophages and lymphocytes to pass through it, whereas fibroblasts cannot pass this basement membrane.[8] The thin mesothelial cell layer and their basement membrane seem to offer very little resistance to the transport of small and large solutes, in vitro or in vivo.[3,12] Thus, the mesothelium does not seem to have any major impact on the transport across the peritoneal barrier under normal conditions.

Interstitium

Beneath the mesothelium lies the interstitial tissue, comprising of an amorphous ground substance or gel like extracellular matrix interlaced with collagenous, reticular, and elastic fibers; adipocytes, fibroblasts, and granular material and containing blood capillaries, nerves, and lymphatic vessels.[13–15] The collagen fibers constitute the largest component of the space between the cells in the peritoneum and form a fibrous skeleton in the interstitium.[15] The collagen fibers bind through β_1-integrins to fibroblasts and other cells in the tissue.[16] The interstitial ground substance may be subdivided into a colloid-rich and a water-rich phase, the two phases being in equilibrium with each other.[3,12,14] The colloid-rich phase contains several different glycosaminoglycans (GAG), including hyaluronan (HA, which is the major component). All GAGs except HA are covalently bound to a protein backbone forming proteoglycans (the combination of a GAG and a protein), for example, chondroitin sulfate, dermatan sulfate, keratan sulfate, and heparan sulfate. The GAGs are polyanionic and have low isoelectric points, and, consequently, the interstitial ground substance has a high density of negative colloidal charge at physiological pH.[14] Water and small solutes can easily enter the colloid-rich phase, whereas macromolecules are excluded from large parts of this phase. In a complex manner, the interstitium may act as a mucopolysaccharide hydrogel, penetrated with more or less continuous channels of free fluid.[3] Whereas small solutes may pass through interstitial matrix hydrogels without much hindrance, the diffusion of macromolecules may be markedly retarded.[5,15] However, it is important to remember that the capillary wall determines the amount of solutes that are transported from blood to interstitium, and both the interstitium and the capillary wall need to be taken into account for the description of the peritoneal transport process.

In general, changes in aggregation and hydration of the ground substance in interstitial tissues affect the physicochemical properties and the functional characteristics of the interstitium,[14] but it is at present not established exactly how peritoneal dialysis may affect the functional characteristics of the peritoneal interstitial tissues.[12] However, thickening of the submesothelial interstitial tissue and fibrosis is common in patients on long-term PD[17,18] and may contribute to the observed long-term changes in peritoneal transport by causing uncoupling between small solute transport and the ultrafiltration coefficient and retarding protein transport.[19]

Capillary Wall

The microvascular exchange vessels in the peritoneal membrane consist of both true capillaries (diameter 5–6 μm) and postcapillary venules (diameter 7–20 μm),[5] and the

capillary wall is considered to be the major transport barrier for transperitoneal exchange of fluid and solutes during peritoneal dialysis. The peritoneal capillaries belong to the continuous type (in which endothelial cells form a continuous layer enwrapped in a negatively charged glycocalyx),[5,20,21] which functionally restrict solute exchange to less than 0.1% of the total capillary surface area (= the small pores, see later).[3,22] However, the exact role of the glycocalyx is controversial.[23–25] The peritoneal capillaries behave functionally as having a heteroporous structure, with a small number of large pores (radius 200–400 Å) through which macromolecules are filtered because of convective flow and a large number of *"small pores"* (radius 40–65 Å), which are impermeable for macromolecules larger than albumin (molecular weight 69,000 Dalton) but do not restrict the passage of small solutes.[20,21,26] In addition, *"ultrasmall"* pores (radius 4–6 Å) were postulated to be involved in the water flow induced by the osmotic effect of low molecular weight osmotic agents, for example, glucose (Figure 26-1).[20,26,27] The anatomical correlate of the water channels was later demonstrated to be aquaporin-1, a protein 28 KDa intramembrane protein shown to be one of the water channels in human proximal tubular cells in the kidney and in various nonfenestrated epithelia.[28,29] Aquaporin-1 has been demonstrated in peritoneal endothelial cells, at mRNA protein, and at functional levels.[30–32] The anatomical correlates to the small pores are possibly the interendothelial clefts.[5,20,26] The three-dimensional structure of the interendothelial clefts has been described in detail.[33] However, the morphological counterpart to the large pores is not established, although it most likely corresponds to larger interendothelial gaps.[5,20,26] Though there has been considerable controversy about the mechanism of macromolecular transport through the endothelium and the potential role of vesicular transport (transcytosis), it is now established that the quantitative role of transcytosis is negligible.[34–36]

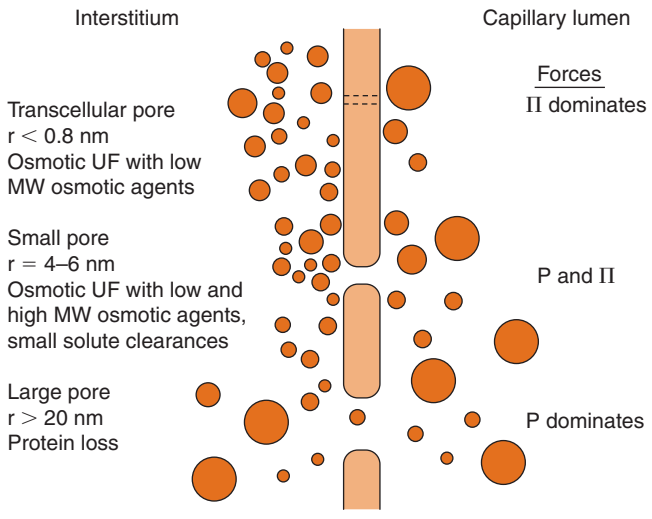


FIGURE 26-1 The three-pore model of peritoneal capillary permselectivity including the transcellular pore (aquaporin-1), the small pore (the interendothelial clefts), and the large pores (possibly large interendothelial clefts). Small circles represent small solutes, and large circles represent proteins. The forces are ∏ (osmotic pressure) and P (hydrostatic pressure). Crystalloid osmotic pressure induced by glucose is very efficient through the transcellular pores, and about 50% of the ultrafiltered fluid will pass through the aquaporins when glucose is used as an osmotic agent in PD. (From M.F. Flessner, Peritoneal transport physiology: Insights from basic research, J. Am. Soc. Nephrol. 2 [1991] 122-135, with permission.)

The three-pore concept of transcapillary exchange[21] has been successfully applied by Rippe and colleagues[20,37–40] to model the peritoneal transport of small solutes and macromolecules and the peritoneal fluid transport, supporting the view that the capillary wall is the main resistance for transperitoneal fluid and solute transport.

PERITONEAL BLOOD FLOW

The mesenteric blood flow is generally supposed to be about 10% of cardiac output.[41] The effective peritoneal blood flow, that is, the blood flow to the capillaries that are directly involved in peritoneal transport, cannot be directly measured.[42] Indirect estimations suggest that the effective peritoneal blood flow may vary from 20 to 40 ml/min (using estimations of the maximal possible ultrafiltration rate) to more than 100 ml/min (based on the measurements of the clearance of gases).[43,44] The effective peritoneal blood flow is generally not believed to limit the clearance of small solutes during peritoneal dialysis,[44,45] because the diffusive mass transport coefficient for urea is approximately 20 ml/min. Also, tracer disappearance from small plastic chambers glued to the serosa was not reduced with a 30% decrease in blood flow and only to a minor degree with no blood flow (in dead rats).[46,47] However, this issue is still controversial, and there are some observations indicating that peritoneal urea clearance may be blood flow limited.[12,42,48] Rosengren and Rippe[49] reported that a reduction of blood flow by 40% (caused by bleeding of rats) resulted in a decreased transport of glucose and[51] r-EDTA by 13% and 24%, respectively. They concluded that there is to some extent a blood flow limitation of peritoneal transport, but that the level of blood flow limitation is much smaller than in other organs. Note that the diffusion rate of small solutes theoretically will not be proportional to the blood flow, but to the square root of perfusion rate, which to a large extent may explain the small change in transport with marked alterations in blood flow.[50] Vasodilators have been shown to increase peritoneal clearances because of a possible increase in the capillary surface area as a result of vasodilatation and recruitment of capillaries.[42,51] Furthermore, changes in the distribution of the blood flow may possibly also affect the peritoneal transport rate.

PERITONEAL LYMPHATICS

The Anatomy of Peritoneal Lymphatics

About 4% of the mesothelial surface area is reported to be covered by lymphatic vessels,[52] but the major part of the lymphatic drainage is considered to occur through the lymphatic stomata in the diaphragmatic part of the peritoneum.[53,54] The diaphragmatic lymphatic stomata, which were first described by von Recklinghausen[55] in 1862, are small openings (diameter 4–12 μm) that are formed by intercellular junctions between both mesothelial cells and lymphatic endothelial cells, and open directly into underlying lymphatic lacunae.[52–54] It is through these specific openings that large particles like erythrocytes and

bacteria can directly leave the peritoneal cavity. The underlying lymphatic plexuses (in which humans are situated mainly on the muscular portion of the diaphragm) intercommunicate directly with the plexuses on the pleural surface through intercommunicating vessels.[53] After leaving the diaphragm, the lymph is drained through the large collecting ducts associated with the internal thoracic vessels to reach the venous circulation through the right lymphatic duct.[53] The lymphatic drainage of the peritoneal cavity is to a large extent dependent on the periodic compression and release of the lymphatic vessels caused by the movements of the diaphragm during respiration.[53,56]

In addition to the lymphatic vessels the diaphragmatic part of the peritoneum, subserosal lymphatic vessels can also be found in other parts of the peritoneal cavity, including the omentum,[53] and, furthermore, local lymphatic vessels are also present in the tissues surrounding the peritoneal cavity, although their role in peritoneal transport seem to be negligible under normal conditions.[53]

Importance of Lymphatic Flow for Peritoneal Fluid Absorption

The disappearance of a macromolecular marker from the peritoneal cavity has often wrongly been used to estimate lymph flow from the peritoneal cavity during peritoneal dialysis. It is now well-established that the peritoneal absorptive flow of fluid and solutes is comprised of two different pathways:[12,57,58] 1) direct lymphatic absorption (mainly through the lymphatic stomata in the diaphragm, and, to a lesser extent, through visceral lymphatic pathways;[58] and 2) fluid absorption into tissues.[20,59] Studies using tracer appearance in plasma have demonstrated that the direct lymphatic flow represents about 20% of the fluid absorptive flow from the peritoneal cavity in clinically stable CAPD patients.[60–62] See later discussion on fluid absorption.

PERITONEAL LOCAL REACTION TO INFECTION

The peritoneal host defense reaction to infection is a complex network of interactions among mesothelial cells, peritoneal macrophages (PMø), dendritic cells, infiltrating neutrophils, monocytes, and other inflammatory cells, and orchestrated by the secretion of vasoactive substances, cytokines, chemokines, growth factors, and components of extracellular matrix.[8,9] The initiation, resolution, and repair process of inflammation in the peritoneal cavity are very complex processes, which presently are under intense study, and the regulation of these processes is starting to be understood.[8–10,63–67]

The initial inflammatory activation by bacteria entering the peritoneal cavity is likely to occur on the mesothelial surface, where mesothelial cells together with PMø have an important role in the initiation of the local immune response.[9] The mesothelial cells are able to contribute to the massive neutrophil influx by generation of chemokines like CXCL8 (previously called interleukin-8), a process that is amplified by the PMø-derived cytokines tumor necrosis factor α (TNFα) and interleukin (IL)-1β;[9,68,69] and the mesothelial cells are also capable of expression of adhesion molecules like ICAM-1, VCAM-1, and PECAM-1 and integrins, which may promote leukocyte attachment to the mesothelial cells.[8] The PMø produced TNFα and IL-1β are thought to be key mediators in the activation of mesothelial cells.[9] The mesothelial cells are the principal source of IL-6 in the peritoneal cavity and synthesize large amounts of IL-6 upon inflammatory challenge.[70] However, mesothelial cells do not express the cognate IL-6 receptor, and therefore they initially are unresponsive to IL-6. There is a rapid accumulation of neutrophils within the peritoneal cavity during the first 12 to 24 hours. The proinflammatory cytokines will also lead to differentiation and activation of dendritic cells precursors in the peritoneum into mature dendritic cells that migrate to the lyphoid tissue to active adaptive immunity.[67] The activated Th1 cells and resident natural killer cells will produce interferon-γ, which upregulates the bactericidal activity of the peritoneal macrophages and is also involved in the recruitment and clearance of neutrophils.[67] Early upregulation of the receptor-interacting protein-2 (RIP2) in peritoneal macrophages is required for the rapid resolution of peritonitis, and RIP2 expression likely is required for the decrease of intracellular infection and regulation of migration of antigen presenting cells.[65,66] RIP2 is a promising biomarker for resolution of peritonitis and may be used in clinic in the near future.[65,66]

After a few days the neutrophils are replaced by a more sustained population of monocytes and lymphocytes.[10] In fact, this temporal switch in the recruitment of leucocytes (which is under a complex regulation) determines whether or not the infection is cleared.[71,72] Liberation of the soluble IL-6 receptor (SIL-6R) from the initial neutrophils allows for the formation of the IL-6 and SIL-6R complex that allows IL-6 responsiveness in cell types (including mesothelial cells) lacking the cognate IL-6 receptor.[71] The IL-6 and SIL-6R complex will downregulate the expression of CXCL8 and other neutrophil-activating chemokines, and the SIL-6R may also directly promote MCP-1 expression resulting in the more sustained mononuclear leukocyte infiltration.[10] In addition, the release of oncostatin M from the infiltrating neutrophils will have a synergistic effect with the SIL-6R for the temporal switch from neutrophil influx to mononuclear cell recruitment as oncostatin M suppresses IL-1β-mediated expression of CXCL8.[63] Interferon-γ also has an important role in this process by control of both the initial neutrophil recruitment independently of IL-6 (through regulation of chemokine expression) and the neutrophils clearance phase by regulating local IL-6 levels.[64,73] The neutrophils will, to a large extent, undergo apoptosis and then be phagocytized by mononuclear cells.[73] This transition from the recruitment of neutrophils (typically associated with innate immunity) to the leukocytes typically associated with acquired immunity is considered to facilitate the successful resolution on the inflammatory reaction.[10,67]

PERITONEAL TRANSPORT PHYSIOLOGY

Barriers to Transperitoneal Exchange

The peritoneum is a complex structure of at least five different resistance barriers coupled in a series: 1) the unstirred fluid layer in the capillaries, 2) the capillary wall (endothelium and basement membrane), 3) the interstitial

space, 4) the mesothelium and its basement membrane, and 5) the unstirred fluid layers in the peritoneal cavity.[74] Each of these barriers has its specific transport properties. The capillary wall is considered to represent the major transport barrier for transperitoneal exchange,[20,26] but the interstitium is also important particularly in long-term PD patients with markedly increased thickness of the submesothelial tissue.[19] The mesothelium, on the other hand, is highly permeable and is not a significant transport barrier.[20,26] The mucopolysaccharide hydrogel of the interstitium will exclude solutes from part of the interstitial water volume and force solutes to follow a tortuous path,[12] and, furthermore, the negative charge of the interstitial ground substance may markedly retard the transport of charged molecules through the interstitium.[14] Unstirred fluid layers in the peritoneal cavity may represent transport resistances for the diffusion of small solutes[12,75] but are likely of much less importance than the interstitium because the diffusibility is much less in the interstitium compared to the stagnant fluid layers.[3,76]

Modeling of Peritoneal Transport

To completely model the peritoneal transport process, all transport barriers and their specific transport characteristics should be taken into account, including the distribution of the capillaries within the peritoneal interstitium. This will result in very complex models that are difficult to apply in the clinical situation, and, at present, even complex models fail to predict ultrafiltration with better accuracy than simpler models.

Single-membrane models have been used to estimate transport parameters in clinical peritoneal dialysis.[77–83] In the single-membrane models, the peritoneal barrier is regarded as a single membrane separating the well-mixed blood and dialysate compartments. The single-membrane models will work very well to describe the transport of small solutes (up to the size of small proteins like β_2-microglobulin) from plasma to dialysate, but they will not work as well for the description of dialysate to plasma transport, and in particular, they cannot correctly describe the osmotic fluid transport when a high molecular solute (e.g., icodextrin) is used as osmotic agent.[5] The distributed model by Dedrick and Flessner[84–86] takes into account the distribution of capillaries in the interstitium and should be preferred from a theoretical point of view. However, the simpler three-pore model by Rippe and colleagues,[37–39] which takes into account the three pore systems in the capillary wall (see earlier text), is still as accurate in predicting both fluid and solute transport during clinical peritoneal dialysis, using both small molecular weight and macromolecular osmotic agents (Figure 26-2).[37,39,87] Also, a model describing the peritoneum as two heteroporous membranes in series (presumably the capillary wall and the

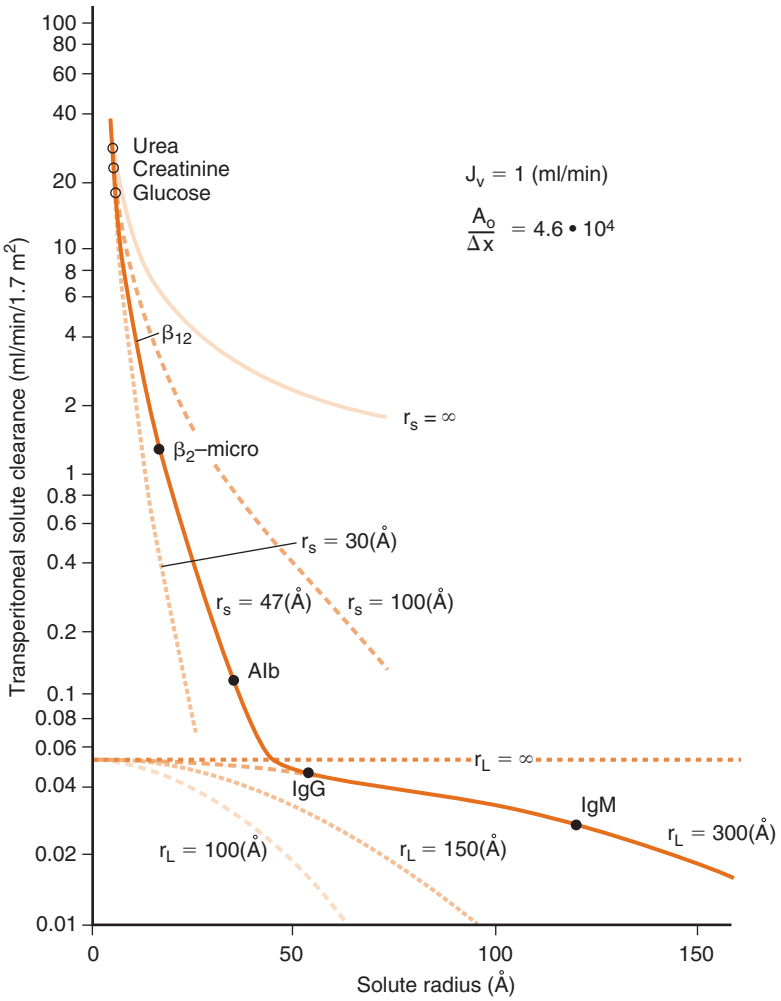


FIGURE 26-2 Semilogarithmic plot of transperitoneal unidirectional clearances versus molecular radius. The solid line represents the theoretic clearances simulated for a small pore radius of 47 Å, a large pore radius of 300 Å, a pore area over unit diffusion distance ($A_0/\Delta x$) of 45,000, and a total blood to peritoneal cavity filtration rate at 1 ml/min/1.73 m^2 body surface area. (From B. Rippe, R.T. Krediet, Peritoneal physiology-transport of solutes, in: R. Gokal, K.D. Nolph [Eds.], The textbook of peritoneal dialysis, Kluwer Academic Publishers, Dordrecht, 1994, pp. 69-113, with permission.)

interstitium) has been developed.[88] This model was further developed based on the current understanding of the long-term changes in peritoneal membrane, combining the concept of the capillary three-pore model with an interstitial fiber-matrix barrier, and has been successful to describe the long-term changes in peritoneal transport of fluid (with uncoupling of small solute transport from the peritoneal ultrafiltration coefficient), and of small and large solutes.[19] The detailed description of the different models lies outside the scope of this chapter.

Fluid Transport

Ultrafiltration

The intraperitoneal dialysate volume over time curves during a peritoneal dialysis exchange are characterized by three phases: 1) initial net ultrafiltration (rate and duration is depending on the osmotic pressure of the solution); 2) dialysate isovolemia (during which ultrafiltration is counterbalanced by fluid absorption); and 3) net fluid absorption (independent on the osmolality of the solution) (Figure 26-3).[89]

Ultrafiltration in peritoneal dialysis is achieved by the application of a high concentration of an osmotic agent (usually glucose) in the dialysate, resulting in a high osmotic pressure gradient across the peritoneal barrier.[12,13,90] However, the osmotic pressure gradient over the peritoneal barrier decreases rapidly because of the absorption of the osmotic agent when small solutes like glucose, amino acids, or glycerol are used as osmotic agents. When a large molecular solute, for example, icodextrin, is used as osmotic agent, the absorption of the osmotic agent is much slower, resulting in a much longer lasting osmotic gradient and positive net ultrafiltration.

Applying the thermodynamic theory of volume transport through selective membranes to the peritoneal membrane, the ultrafiltration rate (Q_U) is directly proportional to the ultrafiltration coefficient (L_PA), which, in turn, represents the product of the hydraulic conductance (L_P) and the effective surface area (A).[13,38,90,91] The ultrafiltration rate is therefore described as:

$$(1) \qquad Q_U = L_PA\,(\Delta P - \sigma_{prot}\Delta\pi_{prot}-)\sum_{i=1}^{n}\sigma_i\Delta\pi_i$$

where ΔP is the hydrostatic pressure gradient, σ_{prot} is the reflection coefficient for total protein, $\Delta\pi_{prot}$ is the colloid osmotic pressure difference caused by the plasma proteins, and the third term within the parentheses represents the sum of all effective crystalloid osmotic pressure gradients across the peritoneal barrier.[38,92,93] Note that this equation is a simplification that applies to the capillary wall and, for the full description of the total process, also local effects in peritoneal tissue (e.g., the distribution capillaries in the interstitium, interstitial tissue pressure gradients) will have an impact on the ultrafiltration rate. Thus the ultrafiltration induced when glucose is used as osmotic agent in PD is dependent on the osmotic pressure difference for glucose, the hydraulic conductance (L_P), the surface area (A), and the reflection coefficient for glucose (σ_g).[38,92,93] A wide range of values for the ultrafiltration coefficient (L_PA) has been reported in the literature because markedly different

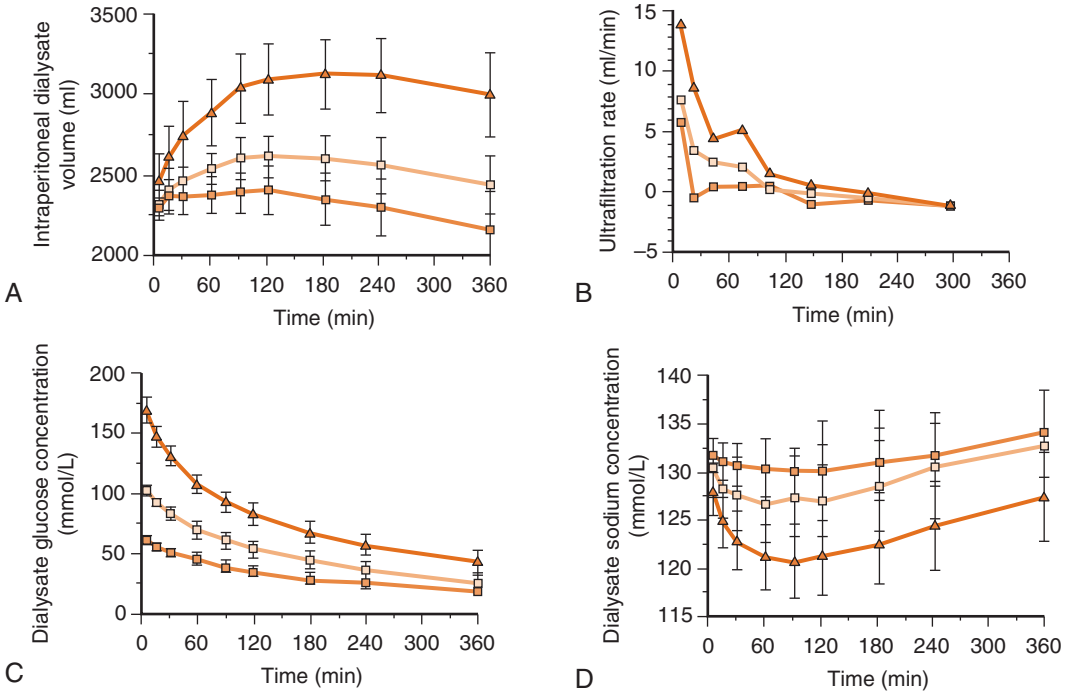


FIGURE 26-3 Intraperitoneal dialysate volume (A), net ultrafiltration rate (B), dialysate glucose concentration (C), and dialysate sodium concentration (D) versus time, during a 6-hour dwell study with an exchange of 2 L of 1.36% (▪), 2.27% (▫), and 3.86% (▲) glucose solution (mean ± SD). The intraperitoneal dialysate volumes were assessed from the dilution of the tracer (radioiodinated human serum albumin) with a correction applied for the elimination of the tracer. Note that when hypertonic 3.86% glucose dialysis solution is used, there is a marked dip in dialysate sodium concentration because of the dilution of the dialysate by the ultrafiltrate. The sodium concentration in the ultrafiltrate is much less than the sodium concentration in plasma because sodium sieving as about half of the ultrafiltered fluid will pass through the aquaporins (From O. Heimbürger, J. Waniewski, A. Werynski, et al., A quantitative description of solute and fluid transport during peritoneal dialysis, Kidney Int. 41 [1992] 1320-1332, with permission.)

values of σ_g have been estimated.[13,78,79,94,95] The reason for these discrepancies is that σ_g in several studies have been calculated as $\sigma_g = 1 - S_g$ (where S_g is the "lumped" glucose sieving coefficient for the whole peritoneal membrane), which is true for homogeneous membranes. However, as the peritoneal membrane is a heteroporous membrane, the relationship between σ_g and S_g may vary.[38] In fact, one of the most convincing arguments for the heteroporous character of the peritoneal membrane is that the direct determinations of L_PA for the peritoneal membrane (assuming $\sigma_{albumin} = 0.9$) in cats and rats (scaled to humans using the scaling factor BW0.7) yielded an L_PA value of approximately 0.1 ml/min/mmHg, which, in turn, yielded a σ_g of approximately 0.02.[92,93] These values are well in agreement with the reported initial ultrafiltration rate of 10 to 20 ml/min with 3.86% glucose solution.[78,79,89,96]

For the peritoneal barrier, the total σ of a solute is equal to the sum of the product of σ and the fractional hydraulic conductivity α for each set of pores. Thus, when applying the three-pore model for the peritoneal membrane, the total σ for a solute will be given by the equation:

$$\sigma = \alpha_A \cdot \sigma_A + \alpha_S \cdot \sigma_S + \alpha_L \cdot \sigma_L \quad (2)$$

where subscripts A, S, and L denote aquaporins, small pores, and large pores, respectively. As the aquaporins are impermeable for glucose, $\sigma_A = 1$ for glucose across the aquaporins, whereas the relative osmotic efficiency of glucose is much less across the small pores ($\sigma_S = 0.03$) and negligible across the large pores (σ_L approximately 0).[39] During normal conditions, the aquaporins account only for a small fraction (approximately 2%) of the LpA, and they will play a minor role in fluid transport, whereas the small pores account for about 90% of LpA. However, when applying a high crystalloid osmotic pressure over the membrane by using a small molecular osmotic agent, the importance of the aquaporins for fluid transport markedly increases. As $\alpha \cdot \sigma$ will be quite similar for the aquaporins ($0.02 \cdot 1 = 0.02$), and the small pores ($0.90 \cdot 0.03 = 0.027$) about half of the ultrafiltration will pass through the aquaporins, resulting in marked sieving of solutes (for the large pores, $\alpha \cdot \sigma$ will approximately be zero as σ_L is approximately 0).[39]

Fluid Absorption

During peritoneal dialysis, ultrafiltration is partly counterbalanced by the peritoneal fluid absorption (Q_A).[38,97–99] Thus the net change in dialysate volume (V_D) is equal to:

$$\frac{dV_D}{dt} = Q_U - Q_A \quad (3)$$

Because Q_A is considered to be a bulk flow, it can be estimated by the disappearance rate (K_E) of a macromolecular marker applied in the dialysate (see reference 99 for a detailed discussion).

Pathways for Peritoneal Absorptive Flow

The peritoneal absorptive flow consists of two different pathways:[12,20,57–59] 1) direct lymphatic absorption (through the lymphatic stomata mainly in the diaphragm, and, to a lesser extent, through visceral lymphatic pathways);[58] and (2) fluid absorption into tissues (where the fluid is absorbed into the capillaries because of the Starling forces, whereas the macromolecules are absorbed slowly through local lymphatics).[20,59] Sieving of macromolecules is assumed to be negligible with the direct lymphatic absorption, and with the second pathway (fluid absorption into tissues), sieving of macromolecules at the site of the mesothelium is considered to be negligible from a practical point of view. Thus the macromolecular disappearance rate from the peritoneal cavity may be used as an estimate of the peritoneal bulk absorptive flow[99] because it is mainly dependent on the two components of peritoneal absorption, which both are considered to be bulk flows.[59,99] When the fluid, which has entered the peritoneal interstitial tissue compartment, is absorbed across the capillary wall (because of the Starling forces), sieving of macromolecules should occur at the site of the capillary wall. It is generally agreed that almost no protein may enter the plasma compartment directly through the capillary wall (although direct capillary uptake of radioiodinated human serum albumin [RISA] has been demonstrated under certain conditions).[21,100] The macromolecules that have entered the interstitial tissue compartment may thus accumulate in the interstitial tissue compartment before they are slowly absorbed by local lymphatics.[59]

The peritoneal absorptive flow is independent of the intraperitoneal osmotic pressure[101] and thus not influenced by ultrafiltration induced by the osmotic agent in the dialysate (i.e., osmotic pressure-driven convective flow). On the other hand, the peritoneal fluid and protein absorption rate in animal experiments have been shown to be directly proportional to the intraperitoneal hydrostatic pressure.[102] Studies by Flessner and colleagues[59,103,104] of tissue concentration profiles of RISA and labeled IgG (absorbed from the peritoneal cavity in rats) strongly support the notion that hydrostatic pressure-driven convection is the most likely mechanism driving the fluid and protein transport into adjacent tissues. It may seem puzzling that osmotic pressure-driven convection during dialysis and hydrostatic pressure-driven convection are considered to go simultaneously in different directions through the peritoneal barrier without any major interaction. However, this apparent paradox may be explained by the nonhomogenous nature of the peritoneal barrier, where different parts have different vascularization, hydrostatic pressure gradients and so forth.[5,57,59] Furthermore, osmotic pressure-driven convection will take place close to the capillaries only, whereas the major part of the peritoneal surface area will allow hydrostatic pressure-driven convection in the opposite direction.[59]

Relative Importance of Lymphatic Absorption and Absorption into Adjacent Tissues

The relative contribution of the two different components of peritoneal absorptive flow (lymphatic absorption and absorption into tissues) has been controversial.[12,20,54,57,59,105] In fact, the disappearance rate of a macromolecular marker has previously been assumed to provide an estimate of the lymphatic absorption rate in peritoneal dialysis patients.[105] However, several studies have shown that the plasma appearance rate of a macromolecular marker is on average only about 10% to 20% of its disappearance rate from the peritoneal dialysate (in clinically stable CAPD patients[60–62,106] and in animals).[104,107,108] Furthermore, studies in animals have demonstrated that a major part of the lost marker

accumulates inside the tissues adjacent to the peritoneal cavity, mainly in the liver, diaphragm, and anterior abdominal wall.[76,103,104,107,109] Thus the interstitial adjacent tissues may serve as a reservoir for RISA from which it is slowly absorbed into local lymphatic vessels.[12,59,104,109]

Theoretically, it is also possible that RISA transport is delayed in lymph nodes compared to the fluid accompanying RISA in the lymphatic vessels.[54] However, trapping in lymph nodes have not been found to be of major importance,[110] and furthermore, this would not explain the high tissue concentrations of macromolecular tracers reported by Flessner and colleagues[103,104] from studies in the rat.

Solute Transport

During peritoneal dialysis, solutes are transported bidirectionally through the peritoneal barrier mainly by diffusion (as a result of the concentration gradient between blood and dialysate) and, to a lesser extent, by convection into the peritoneal cavity (as a result of hydrostatic pressure differences and the osmotic disequilibrium caused by the osmotic agent).[13,89] Also, the solute transport accompanying the convective fluid absorption from the peritoneal cavity (into the surrounding tissues and to blood through the lymphatics; see earlier mention) needs to be taken into account.[13,61,84,107]

Diffusive Transport

Diffusive transport through a membrane is driven by the concentration gradient over the membrane. If diffusion is unrestricted, the solute transfer rate (J_S) is proportional to the concentration gradient between dialysate and plasma (ΔC), the solute's diffusion constant (D, which is inversely proportional to the solutes radius), the surface area available for diffusion (A), and inversely proportional to the diffusion distance (Δx):[3]

$$J_S = \frac{D}{\Delta x} A \Delta C \quad (4)$$

The ratio of the solute's diffusion constant to the diffusion distance ($D/\Delta x$) is called permeability (P), and the product of P and surface area is usually denoted permeability surface area product (PS), which in PD has also been denoted diffusive mass transport coefficient (K_{BD}), mass transfer coefficient (MTC), or mass transfer area coefficient (MTAC). Thus $PS=K_{BD}=MTC=MTAC$. Inserting PS into equation 4 yields the following description of diffusive solute transfer rate for a solute can across the peritoneal barrier:

$$J_S = PS\ \Delta C \quad (5)$$

However, as the peritoneal barrier behaves as a porous structure, the diffusion of a solute may be restricted by the pore passage; the solute has to hit the pore entrance area and the solute may also be restricted by interaction because of friction with the pore wall.[3] The diffusion through the peritoneal barrier will therefore be restricted, and a restriction factor (A/A_0) need to be introduced (where A denotes equal to the apparent pore surface area and A_0 the total cross-sectional pore surface area), and inserting this into equation 4 yields:

$$J_S = \frac{DA}{\Delta x}\Delta C = \frac{DA_0}{\Delta x}\frac{A}{A_0}\Delta C \quad (6)$$

From this it follows that the diffusion rate over the peritoneal membrane for a solute will be governed by the solute's diffusion constant (D), the restriction factor (A/A_0), the concentration gradient (ΔC), and the term $A_0/\Delta x$, that represents the unrestricted pore area over unit the diffusion distance.[3] Because A_0 and Δx cannot usually be determined, $A_0/\Delta x$ will be central term describing the membranes diffusive properties. Knowing $A_0/\Delta x$, the PS can be calculated for different solutes using their diffusion constants (based on the solute radius).[3] Also, when PS is known for one solute, $A_0/\Delta x$ can be estimated and used to estimate PS for other solutes.

Permeability Surface Area Product Under Standard Conditions

Several authors have estimated PS for various small solutes and proteins under standard conditions. The PS values for different solutes decrease with increasing molecular weight, and there seems to be a good agreement between the results from different studies, with reported PS for urea about 18 ml/min, creatinine 10 ml/min, glucose 11 ml/min, inulin 4 ml/min, β_2-microglobulin 1.2 ml/min, albumin 0.12 ml/min, IgG 0.06 ml/min, and α_2-macroglobulin 0.02 ml/min.[3,111,112] The variation in PS from different studies seems to be largest for urea, which is not surprising because dialysate urea concentration is close to equilibration with plasma concentration after 4 hours; the estimated value of PS for urea will be highly dependent on the estimation procedure, in particular, the model applied for PS estimation,[80] and whether or not urea concentrations in plasma are corrected for plasma protein content.[113]

Convective Transport

The magnitude of convective transport is determined by the ultrafiltration rate (J_V) through the peritoneal membrane, the average solute concentration within the membrane (C_M, which for low flow rates is equal to the average of dialysate and plasma concentration), and the sieving coefficient (S, describing the fraction of the solute, which passes through the membrane with the water flow; $0 \leq S \leq 1$). The rate of solute flow through the membrane, J_S, as a result of diffusion and osmotic-pressure induced convection, can be described as:

$$J_S = PS\Delta C + SJ_V C_M \quad (7)$$

Note that solutes are also transported from the peritoneal cavity because of the peritoneal fluid absorption (J_A, vide supra), which is considered to be a bulk flow.[59,99,114] Thus the intraperitoneal solute mass will decrease with a term proportional to J_A and C_D. The net solute flow to the peritoneal cavity (Q_S) is equal to:[115]

$$Q_S = PS\Delta C + SJ_V C_M - J_A C_D \quad (8)$$

For the peritoneal barrier, the sieving coefficient for small solutes will be dependent of the fraction of ultrafiltration that passes through small and large pores in relation to the total ultrafiltration flow (through aquaporins, small pores,

and large pores), because no solutes will pass through the aquaporins and the convective passage of small solutes through the other pores will not be subject to any sieving.

Importance of Different Parts of the Peritoneum for Peritoneal Transport

Different parts of the peritoneal barrier may have different transport characteristics. These differences will influence the relative importance of different parts of the peritoneum on the total solute and fluid transport through the peritoneal barrier. In particular, the permeability, distribution, and surface area of the capillaries within different parts of the peritoneal membrane may have an impact on the relative importance of different parts of the peritoneal membrane for the overall fluid and solute transport.[48] Furthermore, the mixing of dialysate may be different in different parts of the peritoneal cavity, with particularly poor mixing in pockets of the visceral peritoneum, which may decrease solute transport in regions of the peritoneal cavity where mixing is poor.[6] This is likely one reason why studies of peritoneal transport after evisceration suggests that the hollow viscera may play only a minor role in the overall peritoneal transport because evisceration was found to reduce absorption of urea, creatinine, glucose, and inulin only by about 10% to 20% despite removal of approximately 60% of the peritoneal surface area during experimental peritoneal dialysis in rats.[116] After evisceration the contact between dialysate and the membrane is likely to be improved in some areas because of redistribution of fluid to areas not accessible to the dialysate before evisceration.[48]

The parietal peritoneum seems to have only a minor role in peritoneal solute transport, because shielding of the parietal wall with plastic patches did not affect the overall peritoneal transport of urea, creatinine, glucose, or inulin.[116]

The role of different parts of the peritoneal membrane for lymphatic absorption has been studied by Rippe and colleagues[117] by measuring the peritoneal to plasma clearance of I^{125}-RISA in rats after evisceration, or after sealing the diaphragm or the anterior abdominal wall with histoacrylate glue, compared to control rats. They concluded that lymphatic absorption mainly occurs (60%) through diaphragmatic pathways, whereas about 30% occurs through visceral lymphatic pathways, and just a small fraction passes through parietal tissue pathways. On the other hand, the total bulk fluid absorption from the peritoneal cavity (as assessed by the disappearance of RISA) decreased markedly after sealing of the anterior abdominal wall, indicating that the anterior abdominal wall plays an important role in peritoneal fluid absorption.[117] This is in agreement with the studies by Flessner and colleagues[103,104,107] demonstrating that a significant portion (28%) of the tracer leaving the peritoneal cavity is absorbed into the anterior abdominal wall, resulting in local tracer accumulation within the tissues of the anterior abdominal wall.

Tests to Assess Peritoneal Transport

There are several tests available for the assessment of peritoneal transport characteristics. There are commercial computer programs available to assess basic peritoneal transport parameters and to predict effects of various treatment schedules on peritoneal small solute clearances and ultrafiltration.[40,118–121] In general, the results will be closely dependent on the quality of data used for calculations or put into the computer. In particular, if only long dwells are used and the solutes are close to equilibration, it will be impossible to calculate transport characteristics (see later text). The lab methods may also be very important for the results, and, in particular, creatinine levels in dialysate measured with the Jaffé method must be corrected for the interference with high concentrations of glucose in dialysate.[122] Sodium levels should preferably be measured with flame photometry or indirect ion-selective electrodes, because measurements with direct ion-selective electrodes may give different results.[123,124]

Diffusive Mass Transport Coefficients

For small solutes, the diffusive mass transport coefficient PS ($=K_{BD}=MTC=MTAC$, see previous text) can be assessed with high accuracy using equation 8, if the sieving coefficients and the volume flow is known. If there are no large volume changes, PS can easily be determined using the solute concentrations in dialysate at the beginning (C_{D1}) and in the end of a dwell (C_{D2}), the solute concentration in plasma (C_P):[3,125,126]

$$PS = \frac{\bar{V}}{t_2 - t_1} \ln \frac{C_P - C_{D1}}{C_P - C_{D2}} \quad (9)$$

Where t_1 and t_2 are start and end of the exchange, respectively, and $\bar{V}$ is the average volume during the exchange. This equation has been widely used for the estimation of PS but should be used only when there is a low ultrafiltration rate. Also, it is important to note that the result is closely dependent on the difference between solute concentration in dialysate and plasma at the end of the dwell. Therefore, when using this method, solute concentration in plasma (C_P) should be preferably recalculated to achieve the concentration in plasma water (C_{PW}) by correcting for plasma protein and lipid content to avoid overestimation of PS.[126] This can be done using the equation:[113]

$$C_{PW} = C_P \frac{1}{1 - V_{Lip} - 0.000718 \cdot C_{prot}} \quad (10)$$

where V_{lip} is the fractional volume for lipids (often approximated to 0.016) and C_{prot} is the concentration of total protein (often approximated to 65 g/L) in plasma. However, for solutes that are almost equilibrated at the end of an exchange, this method should still not be used, because small random errors in solute concentration will result in large variations in PS. Instead, a shorter dwell time (when the solute concentrations are not equilibrated between dialysate and plasma) should be used for estimation of PS.

There are also much more sophisticated methods to estimate PS for small solutes, but results agree quite well bearing the limitations of different methods in mind. Presently, computer software is available for the calculation of PS.[40,118–121]

Peritoneal Equilibration Test

The most widely used approach to evaluate peritoneal transport characteristics in individual patients is to measure the dialysate to plasma solute concentration ratio (D/P) for

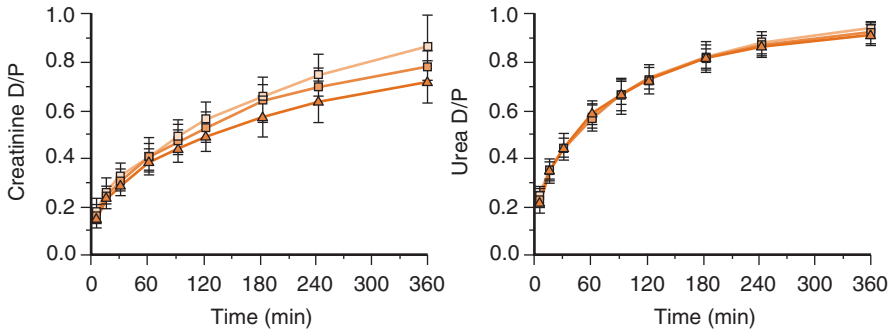


FIGURE 26-4 Dialysate to plasma equilibration curves (mean ± SD) for creatinine and urea during a 6-hour dwell study with an exchange of 2 liters of 1.36% (□), 2.27% (□), and 3.86% (△) glucose solution. (From O. Heimbürger, J. Waniewski, A. Werynski, et al., Dialysate to plasma solute concentrations [D/P] versus peritoneal transport parameters in CAPD, Nephrol. Dial. Transplant. 9 [1994] 47-59, with permission.)

particular solutes during an exchange with conventional peritoneal dialysis fluid (Figure 26-4).[89] This procedure (which was first proposed by Verger)[127] has been standardized in the peritoneal equilibration test (PET) by Twardowski and colleagues[122] and has won wide acceptance as a routine method to assess clinically important alterations in peritoneal transport characteristics. The PET procedure is standardized as regards sampling procedures, duration of dwell, evaluation of the results, and so forth.[122,128,129] Briefly, the overnight dialysate is drained and 2 L of 2.27% glucose dialysis fluid are infused. The original PET description included several dialysate samples,[122] but usually, the procedure is simplified and dialysate samples are taken after infusion, and then after 2 and 4 hours, at which time the dialysate is drained and the volume recorded. A blood sample is drawn at 2 hours dwell time. Usually, the dialysate drainage volume (used as a measure of ultrafiltration capacity), D/P for creatinine, and D/D_0 (dialysate concentration/initial dialysate concentration) for glucose are compared to standard values. The D/P for creatinine and D/D_0 for glucose from the PET will be closely related to the diffusive mass transport coefficient for these solutes.[130] The patients are usually classified according to D/P creatinine at 4 hours using Twardowski's initial classification into different transport groups (Table 26-1).[111,118,122,128,131–134]

It has been suggested to use 3.86% glucose solution instead of 2.27% glucose solution for the PET because it will give a better estimate of ultrafiltration capacity because the ultrafiltration rate is higher and the discrimination between patients better. Thus the net ultrafiltration will be less dependent on variations in residual volume between the start and end of the dwell, and the use of more hypertonic solution also makes it possible to use decrease in dialysate sodium as an additional parameter to identify patients with poor ultrafiltration.[135–140] When hypertonic 3.86% glucose dialysis solution is used, there is a marked dip in dialysate sodium concentration because the sieving and sodium and about half of the ultrafiltered fluid will pass through the aquaporins (see earlier text) (see Figure 26-3). In patients with normal transport characteristics, the decrease in dialysate sodium is marked during the first 60 minutes, then it decreases slightly to reach its lowest value after approximately 90 minutes, and thereafter the dialysate sodium concentration increases because of sodium diffusion from plasma.[89]

PET is a simple procedure and easy to perform, the standard values are well-established, and it does not require any complicated calculations. On the other hand, the D/P and D/D0 results are rather sensitive to laboratory errors (only three samples are used), and the net ultrafiltration (measured as drained minus infused volume) is sensitive to variation in the intraperitoneal residual dialysate volume because of incomplete drainage. Furthermore, PET does not provide any details of the peritoneal transport process. However, a commercial computer software program (PD-Adequest) has been developed using results from the PET and the preceding overnight exchange to allow for calculation of basic transport parameters and to simulate the effects of changes in treatment schedules in individual patients.[40,121] The PET has also been modified by using more frequent sampling and adding a tracer to the dialysate to allow for more detailed analysis of changes in intraperitoneal volume.[141]

TABLE 26-1 Characteristics of the four different peritoneal solute transport groups as classified by D/P creatinine after 4 hours of a peritoneal equilibration test, according Twardowski's initial classification.[112]

TRANSPORT CATEGORY**	4 h PET D/P CREATININE[122,128]	MINI-PET WITH 3.86% GLUCOSE[134]	$A_0/\Delta X$[118] (cm/1.73 BSA)	UF[128]	STANDARD CAPD 2 L X 4/24 h[111,131] Kt/V	CREATININE CLEARANCE	APD COMPARED TO CAPD[132] Kt/V[a]	CREATININE CLEARANCE[a]
Fast	>0.81	>0.52	>30,000	↓↓	=	↑↑	↑↑	↑↑
Fast Average	0.65–0.81	0.43–0.52	23,600–30,000	↓	=	↑	↑↑	↑↑
Slow Average	0.5–0.65	0.34–0.43	17,200–23,600	↑	=	↓	↑↑	= – ↑
Slow	<0.5	<0.34	<17,200	↑↑	=	↓↓	↑	= – ↓

[a]The resulting clearances from APD will be strongly dependent on the APD prescription. The table is based on an APD prescription with a total dialysis fluid volume of about 15–20 L for APD and a wet day with an additional daytime exchange.
**The transport categories have previously been denoted high, high average, low and low average, but it is now recommended to use fast, fast average, slow average and slow peritoneal transport instead.

The D/P values generated by the PET procedure show an excellent correlation with the diffusive mass transport coefficient PS for small solutes, and PS and D/P for creatinine and PS and D/D0 for glucose can be used to identify patients with loss of ultrafiltration capacity because of increased diffusive transport.[136] When using 2 L of 4.25%/3.86% dextrose/glucose solution for the PET, it was suggested to define loss of ultrafiltration capacity as a net ultrafiltration below 400 ml after 4 hours.[137] This definition has won wide acceptance, and the use of hypertonic solution for the PET is strongly recommended for the evaluation of UF capacity.

Mini-PET and Double Mini-PET Recently, a short 1 hour "mini-PET" with hypertonic 3.86% glucose solution was suggested for the evaluation of ultrafiltration and free water transport.[134] It was also found to give estimates of solute transport (D/P creatinine) and classification of patients into different transport groups in good agreement with a 4 hour PET. In addition, free water transport could be estimated from the net ultrafiltration and sodium removal.[134] A further improvement of this test was done by combining two consecutive 1 hour mini-PETs (with 1.36% and 3.86% glucose solutions, respectively) in the double mini-PET. This approach gives the possibility to calculate an estimate of the free water transport, the osmotic conductance for glucose, and the ultrafiltration through the small pores. The double mini-PET seems to be a simple, fast, and useful test, in particular for the evaluation of patients with reduced ultrafiltration capacity.[142]

Personal Dialysis Capacity Test

The personal dialysis capacity (PDC) test involves urine, blood, and dialysate sampling. The patient collects urine and dialysate during a standardized CAPD-day using a special exchange schedule, with two short (2 to 3 hours) and two medium long exchanges (4 to 6 hours), each with two different glucose solutions, and one long overnight exchange. A sample is taken from each bag and the volume of each bag is measured to give the variation in net ultrafiltration and solute equilibration with time and with the two glucose-based dialysis fluids.[118,120,143,144] The data are put into a special software program, Personal Dialysis Capacity (PDC), based on the three-pore model of peritoneal transport and calculates the following transport parameters (in addition to adequacy parameters and residual renal function): 1) area parameter ($Ao/\Delta x$), determining the diffusion capacity of small solutes, and indirectly, the hydraulic conductance of the membrane (LpA); 2) reabsorption rate of fluid from the peritoneal cavity to the blood after peak time, when the glucose gradient has dissipated; and 3) large pore fluid flow, which determines the loss of proteins to the PD-fluid. The $Ao/\Delta x$ is a more general parameter than PS for a specific solute and can be also used to classify the patients into similar transport groups as the PET (see Table 26-1). Because the PDC is based on five different determinations of dialysate concentration, it should have better and more reliable classification of individual patient's transport rate, if a correct sampling procedure has been carried out.[120,143,144]

Peritoneal Transport Groups

Peritoneal dialysis patients are usually classified according to D/P creatinine at 4 hours of the PET using Twardowski's initial classification into high transporters (above mean + 1 SD), high average transporters (between mean and mean + 1 SD), low average transporters (between mean and mean − 1 SD), and low transporters (below mean −1 SD), but this classification may also be done using the PDC "area" parameter (see Table 26-1).[118] However, preferably fast and slow transport should be used instead of high and low because the net removal of very small solutes (e.g., urea) is often low in "high" transporters as a result of poor ultrafiltration and lower drained volume. Fast and fast average transporters have more rapid equilibration of creatinine and poorer net ultrafiltration because of more rapid glucose absorption, whereas slow average and slow transporters will have lower solute transport, resulting in slow glucose absorption and high net ultrafiltration but low peritoneal clearances for creatinine and larger solutes. Usually, Twardowski's initial limits[122,128] are used to define transport groups, although most studies show an average creatinine D/P equilibration rate that is more rapid than in the study of Twardowski.[145–147] It is also likely that there are different types of fast transporters.[148–150] See later discussion.

Effluent Soluble Markers of the Peritoneal Membrane

In addition to solutes originating from the circulation, the drained peritoneal dialysate also contains substances that are locally produced or released from the surrounding tissues or from cells released into the dialysate. These substances include lubricants and surface tension-lowering substances, such as phospholipids, various cytokines, growth factors, chemokines, prostanoids, and constituents of the extracellular matrix (e.g., glycosaminoglycans and procollagen peptides), and also coagulation, fibrinolytic, and antithrombogenic substances.[151] Some of these substances have been measured in effluent dialysate to better understand to the local intraperitoneal immune system and the local reaction to complications like peritonitis, and the concentrations of some of these substances have also been used as markers of the peritoneal membrane status in apparently stable PD patients. However, it should be noted that the interindividual variation is very large even in clinically stable patients without overt complications, and surprisingly little data are available on the long-term evolution of these markers in patients treated with PD. It should also be stressed that appearance rate (i.e., the amount of solute in the drained bag multiplied with the drained volume and divided by time) should be used when comparing patients, and not the concentration, if there is a marked interpatient variation in drained volume or dwell time. Otherwise, the marker concentration may vary because of differences in dilution as a result of differences in infused volume or in net ultrafiltration, for example.

The most widely used marker of membrane status in clinical studies has been the dialysate effluent concentration of cancer antigen 125 (CA125).[152] CA125 is a 220 kD glycoprotein produced by mesothelial cells, and the CA125 level in dialysate increases linearly with dwell time and correlates with the number of mesothelial cells in the effluent. Patients on long-term PD and patients with peritoneal sclerosis have low levels of dialysate CA125.[153] Based on these observations, CA125 has been suggested to be a marker of the mesothelial cell mass or turnover in stable CAPD patients.[152] Increased levels of dialysate CA125 have widely been used as a marker of

improved biocompatibility of new PD solutions, and effluent levels of CA125 consistently increase with the use of more biocompatible dialysis solutions in clinical studies.[154,155] However, the interpatient variation in dialysate CA125 is large, and it is not completely clear exactly what it represents. Therefore, the CA125 levels in dialysate effluent need to be interpreted with some caution.

Another interesting effluent candidate marker of peritoneal membrane health status during long-term PD is hyaluronan (HA), which is an important constituent of the interstitial tissue and is produced by mesothelial cells and fibroblasts. HA is involved in several physiological processes, such as tissue repair and wound healing. The fraction of HA that is produced by mesothelial cells forms a coat on the mesothelial cells together with other glycosaminoglycans and phospholipids. HA concentration increases with intraperitoneal inflammation and decreases with use of more biocompatible PD solutions.[155,156] The procollagen peptides, procollagen-1-C-terminal peptide and procollagen-3-N-terminal peptide, are produced locally by fibroblasts and mesothelial cells during the synthesis of collage 1 and 3, respectively, and have also been measured in dialysate as potential markers of local collagen synthesis,[154,155] but it is not completely clear what the levels represent.

Other potentially important markers are the central proinflammatory cytokine IL-6 and its soluble receptor (sIL-6R) because of their central role in the regulation of intraperitoneal inflammation.[10,157] Also, increase in effluent IL-6 has been reported to relate to increasing peritoneal transport rate for small solutes.[157] Vascular endothelium growth factor (VEGF) is also a potentially interesting marker, because it enhances vascular permeability and angiogenesis, and it is upregulated in peritoneal capillary endothelium in long-term PD patients.[158] Interestingly, both IL-6 and VEGF decrease with the use of more biocompatible solutions.[156]

Factors Affecting Peritoneal Transport

A number of factors have been shown to influence peritoneal transport, possibly by altering the underlying physiological conditions that govern the exchange rate between blood plasma and dialysate. In particular, vasodilatory factors have been shown to increase peritoneal clearances as a result of a possible increase in capillary surface area available for transperitoneal exchange.[159]

Temperature

Klapp[160] reported in the beginning of the last century that heating the anterior abdominal wall resulted in increased fluid absorption from the peritoneal cavity, whereas the opposite effect was noted with cooling of the abdominal wall. The effect of increased temperature was possibly mediated through local vasodilation because local hyperemia could be observed at the serosal and parietal peritoneum.[160] An increase in dialysate temperature will also result in an increased solute transport, in addition to the increased fluid absorption.[161]

Intraperitoneal Hydrostatic Pressure

The intraperitoneal hydrostatic pressure is the driving force for convective movement of fluid and solutes into the adjacent tissues.[59] The hydrostatic pressure increases with increasing intraperitoneal dialysate volume[162–164] and varies with body position; the pressure is higher in sitting and standing than in supine position.[162] The intraperitoneal hydrostatic pressure seems to increase in almost linear fashion with increased and infused dialysis volume in PD patients,[162,163] but a study in rats using a larger variation in infused dialysate volume shows that this relationship, in fact, seems to be exponential.[164]

The increased intraperitoneal pressure results in increased fluid absorption,[165] mainly because of increased fluid absorption into adjacent tissues and not increased lymphatic absorption, because the peritoneum to plasma clearance of a radioactive tracer was unchanged when the intraperitoneal pressure was increased in a study in rats.[166] In agreement with these findings, Durand and colleagues[167,168] reported on a negative correlation between net ultrafiltration and intraperitoneal pressure at the end of a 2-hour dwell in stable CAPD patients.

Dialysate Volume

In a systematic study of infused dialysate volumes between 0.5 and 3 liters in 10 stable PD patients, Keshaviah and colleagues[169] found that PS for urea, creatinine, and glucose increased in an almost linear fashion between 0.5 and 2 L infused volume, its values almost doubling over this range. Between 2 and 3 L infused dialysate volume, there was only a small increase in PS values. However, infused volumes yielding maximum urea PS were found to increase with increasing body surface area. The authors attributed the increase in PS to a more effective contact between dialysate and the peritoneal surface area.[169] Krediet and colleagues[170] studied the effect of a 3-L exchange compared to a 2-L exchange with 1.36% glucose solution and reported on significantly higher PS for creatinine, kanamycin, and inulin with the larger volume, but no difference in PS for urea, lactate, glucose, β_2-microglobulin, albumin, or IgG was found. However, the net ultrafiltration relative to the volume at 5 minutes was lower at almost all occasions because of a markedly increased fluid absorption rate with the 3-L exchange volume, possibly related to an increased intraperitoneal hydrostatic pressure.[170]

Effect of Body Posture on Peritoneal Transport

The effect of upright body position have been addressed in a few studies showing a slightly slower D/P equilibration and a decreased net ultrafiltration rate in sitting or standing compared to recumbent position.[171,172] The slightly slower transport rates are due likely to a decreased contact between dialysate and the peritoneal membrane in sitting position as ultrasound investigation revealed that the bulk of the dialysate was found in the subumbilical region of the peritoneal cavity,[171] and the reduced net ultrafiltration is due to an increased peritoneal fluid absorption as a result of an increased hydrostatic pressure in upright position compared to supine position.[172] Upright position will also increase the hydrostatic pressure gradient over the anterior abdominal wall, where a large part of the convectively induced peritoneal absorption takes place.[59]

Effect of Dialysate Composition on Peritoneal Transport

Several factors related to the peritoneal dialysis solutions per se may also affect peritoneal transport, for example, hyperosmolality, type and concentration of osmotic agent applied, pH, type of buffer, buffer concentration, glucose degradation products, and other contaminants.

Glucose Concentration and Osmolality

As hyperosmolality is a known vasodilatory factor,[173] it is reasonable to expect that hyperosmolality may induce changes in peritoneal transport rates. The use of a 7% glucose solution for peritoneal dialysis in uremic patients was associated with an increased solute clearance (compared to 1.5% glucose solution), which exceeded the possible contribution of convective transport,[174,175] and similar effects have been found in animal studies. In contrast, the clinical use of the presently available hypertonic 3.86% (anhydrous glucose, corresponding to 4.25% of hydrous glucose) dialysis solutions does not seem to affect the peritoneal diffusive transport characteristics in peritoneal dialysis patients.[89]

In addition, during heat sterilization and storage of glucose containing peritoneal dialysis solutions, several toxic glucose degradation products (GDPs) are formed, for example, formaldehyde, 3-deoxyglucosone, 3,4-Dideoxyglucosone-3-ene, and several other low molecular weight aldehydes.[176–179] Although GDPs do not seem to have any major acute effect on peritoneal transport in the concentration found in currently used peritoneal dialysis solutions, these pollutants are likely involved in the evolution of the changes in peritoneal structure and function observed in the long-term PD patients.[180]

Alternative Osmotic Agents

In general, osmotic agents with a lower molecular weight compared to glucose, for example, amino acids and glycerol, will be absorbed more rapidly than glucose, resulting in a shorter period of positive net ultrafiltration than with glucose solutions of the same osmolality.[181–183] However, the presently available amino acid solution will induce similar, or slightly better, ultrafiltration compared to 1.36% glucose solution because of the slightly increased osmolality of the amino acid solution.[184,185] Although the use of the presently available 1.1% amino acids solution does not seem to affect peritoneal transport using the PET,[186] they seem to slightly increase peritoneal solute transport and blood flow in one study,[187] and hypertonic 2.7% amino acid solution has also been reported to be associated with slightly increased peritoneal transport rates.[183,188]

Several large molecular weight osmotic agents, such as starch, glucose polymers, dextran, gelatine, albumin, and polypeptides, have been used in experimental studies.[189] Because the capillary wall is easily permeable to water and small solutes but restricts the passage of large molecular weight solutes, the osmotic effect of colloid during peritoneal dialysis is much more prolonged than the osmotic effect of small solutes. Therefore, even with a relatively low osmolality, the colloid osmotic pressure may ensure the sustained osmotic transport of water.[190] Note that the main osmotic effect of the polymers will occur over the small pores, and sodium sieving will thus not be observed.[87]

Icodextrin, which is the only commercially available large molecular weight osmotic agent in clinical practice, is a specific fraction of dextrin isolated by fractionation of hydrolyzed cornstarch.[191] Icodextrin is a polydispersed mixure of polymers with varying chain lengths, with the majority of icodextrin polymers (>85%) have a molecular weight between 1680 to 45,000 Daltons. The osmotic pressure from icodextrin will be relatively high over the small pore system because icodextrin cannot pass through the small pores, whereas the water flow through the aquaporins will be small because of the low difference in osmolarity and the small total area of the aquaporins. As the ultrafiltration with icodextrin solution will occur almost entirely through the small pores, no sieving of small solutes will be observed with this solution.

The presently used 7.5% icodextrin solution is in fact hypoosmolar compared to plasma but will result in a sustained net ultrafiltration for more than 14 hours because of the sustained colloid osmotic gradient.[87] The icodextrin-based solution does not affect peritoneal solute transport characteristics,[192,193] but the large osmotic fluid flow through the small pores will result in increased clearance of sodium and of low molecular proteins like β_2-microglobulin and leptin.[87,193,194]

Absorption of icodextrin occurs primarily because of the relatively slow convective fluid movement out of the peritoneal cavity.[195] As a result the absorption of the osmotic agent is much slower, resulting in a longer duration of the osmotic gradient and a positive net ultrafiltration. Thus the osmotic pressure created by icodextrin will be relatively constant during the dwell and UF is sustained throughout the long dwell.[87,190,192,193,196] Only about 20% to 40% of the administered icodextrin is absorbed from the peritoneal cavity during a long dwell.[195–197]

Because of the slow absorption of icodextrin and the sustained ultrafiltration with icodextrin solution, it is theoretically well suited for patients with poor ultrafiltration because of rapid glucose absorption. Several clinical studies also demonstrate that this is the case also in the clinical situation[198–200] where icodextrin solution can provide good ultrafiltration also in these patients. In contrast to the decline in ultrafiltration with glucose-based solutions during peritonitis episodes, icodextrin solution will preserve its ultrafiltration capacity also during peritonitis.

Effect of pH and Different Buffers on Peritoneal Transport

Conventional glucose-based dialysis solutions were reported to be vasoactive (when applied directly to capillaries) with an initial transient vasoconstriction (for less than 2 minutes) followed by a maximal vasodilatation sustained during the whole study period.[201,202] The high osmolality or high concentration of buffers, acetate, or lactate were indicated as possible factors.[201,202] The unphysiologically low pH in traditional dialysis fluids is also considered to be vasoactive and may thus theoretically influence the vascular responses in the peritoneum during dialysis. A few studies have been conducted to assess the effect of pH per se on peritoneal transport. However, the low pH in dialysis fluids was not found to induce distinguishable vasoactive responses in the

peritoneum[202] or to affect the peritoneal solute transport characteristics in rats[203,204] or humans.[205,206]

Acetate, lactate, and bicarbonate have been used as buffers in peritoneal dialysis solutions. As pH and other factors may also differ between solutions with different buffers, it is difficult to assess the possibly independent effects of pH and buffer on peritoneal transport. Furthermore, the long-term effects of the dialysis solution on peritoneal transport seem to differ between similar solutions produced by different manufacturers,[207,208] and it is possible that differences in their production processes may have resulted in differences between the solutions, for example, in different content of GDPs.

Acetate was previously used as a buffer in dialysis fluids. However, although acetate buffered solutions seem to have no effect on peritoneal UFC in short-term studies,[209] long-term use of acetate was associated with high frequency of ultrafiltration capacity failure[207,210,211] and has, furthermore, been suggested to be implicated in the etiology of encapsulating peritoneal sclerosis (EPS, previously called sclerosing encapsulating peritonitis).[212] However, use of acetate-based solutions from different manufacturers were associated markedly different risks for EPS, suggesting that also other factors were different between the solutions.

Because of the side effects of acetate solutions, lactate was for many years the almost exclusively used buffer in commercially available peritoneal dialysis solutions. At present, different bicarbonate solutions are available, and the transport does not seem to differ to a major extent in clinical studies among lactate, bicarbonate/lactate, or pure bicarbonate solutions.[205,213]

Effect of Biocompatible Solutions on Peritoneal Transport

During the last decade, several new, more biocompatible PD solutions have been introduced. These solutions are characterized by more physiological characteristics with neutral pH, by markedly reduced content of glucose degradation products, and in some cases by use of bicarbonate as buffer (either in combination with lactate or pure bicarbonate).[214] These solutions have got a wide spread use in some areas of the world in the hope that they will be beneficial in the long-term preservation of the structure and function of the peritoneal membrane. However, so far this is not established. Several randomized medium-term studies (up to 24 months) of biocompatible PD-solutions have been performed, but it is obvious that this time period is too short to study the long-term effects of changes in peritoneal function. However, most of these short-term studies show either no effects or small effects on peritoneal transport with a slight increase in small solute transport and a slightly reduced ultrafiltration in some of the studies.[155,215–224] These effects seem to be rapid and disappear relatively shortly after switch back to traditional bioincompatible solutions.[215,219] However, use of new biocompatible solutions is associated with increased effluent levels of CA-125, suggesting increased mesothelial cell turnover or cell mass.[155,215,223] Though mechanisms behind the changes in peritoneal transport with biocompatible solutions remain elusive, it is possible that the effect of the solutions on the mesothelial cell may in turn affect the peritoneal capillaries and turn the effective peritoneal surface area.

Pharmacological Effects on Peritoneal Transport

Several drugs and hormones have been reported to alter peritoneal transport rates.[42,51,159,225] The results of many of these studies must, however, be interpreted with caution because the experimental conditions are not always standardized, and several other factors may also have been altered by the experimental conditions. Also, accurate determinations of dialysate volume are often lacking.[226]

Vasoactive Drugs

Intravenous administration of norepinephrine significantly decreases peritoneal clearances, whereas dopamine increases the peritoneal solute transport rate, possibly because of vasodilation caused by stimulation of mesenteric dopamine receptors.[225] In general, vasodilatory drugs have been reported to increase peritoneal transport;[42,51,159,227,228] for example, theophylline, furosemide, hydralazine, and sodium nitroprusside (a nitric oxide donor) have all been reported to augment peritoneal clearances—an effect that is possibly related to an increased peritoneal capillary surface area. On the other hand, splanchnic vasoconstrictors, like norepinephrine,[229] generally tend to decrease peritoneal clearances.[159]

Changes in Peritoneal Transport During Peritonitis

Peritonitis is associated with several changes in peritoneal transport. A fall in ultrafiltration capacity (UFC) is often noted during peritonitis,[230–232] but this alteration is transient and UFC usually returns to normal within less than 1 month.[230,233]

The decreased UFC is most commonly associated with increased small solute transport and rapid glucose absorption and consequently loss of the osmotic driving force.[230,232] In addition, the peritoneal fluid absorption is markedly increased.[118,234] Detailed studies of peritoneal fluid absorption have not been performed, but it is likely that the increase in fluid absorption is due to both increased lymphatic flow and increased convective fluid transport into adjacent tissues.[111]

The increased small solute transport seems to be related to an increased peritoneal capillary surface area, probably as the result of inflammatory recruitment of microvessels.[39,118] This effect is likely, to a large extent, mediated nitric oxide (NO) and both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS), which have been demonstrated to be markedly upregulated in a rat model of acute peritonitis with poor ultrafiltration and increased small solute transport.[235] Also, the structural changes, the increased solute transport, and the poor ultrafiltration were much less pronounced in eNOS knockout mice.[236]

Furthermore, peritonitis is associated with markedly increased protein losses in dialysate,[118,230–232] indicating an increase in the number or size of the large pores.[118] The intraperitoneal production of prostaglandins (e.g., PGE2 and PGI2) is increased during peritonitis.[231] As the increased peritoneal protein loss during peritonitis correlates with the increased dialysate concentration of prostanoids,

and, furthermore, as the increased protein loss partly may be inhibited by indometacin,[231] it may be suggested that the increased peritoneal protein loss during peritonitis is mediated, at least partly, by the vasoactive prostaglandins.

Changes in Water and Solute Transport with Time on Peritoneal Dialysis

Changes in peritoneal solute transport are common after initiation of peritoneal dialysis. Several studies using the PET have reported on a significant increase in 4-hour D/P creatinine from the PET after 6 months of CAPD compared to initial results obtained during the first 2 weeks of CAPD, whereas ultrafiltration was rather stable.[237–240] It has also been reported that in patients with initially high solute transport, transport rate may in fact decrease.[240,241]

Changes in Peritoneal Transport with Long-Term Peritoneal Dialysis

In the majority of patients treated with CAPD for up to 3 years, the peritoneal UFC and small solute transport characteristics seem to be relatively stable,[240,242,243] although several studies demonstrate a tendency toward increasing diffusive mass transport coefficients for small solutes and a tendency toward decreasing net UF.[237,239,240,243–245] However, individual patients may behave markedly different; some patients demonstrate increased diffusive solute transport and decreased ultrafiltration, whereas other patients show opposite patterns.

In patients treated with PD for 4 years or more, the tendency toward decreasing ultrafiltration and increasing small solute transport is evident in almost all prospective studies.[237,246] In contrast, macromolecule transport (as assessed by protein clearances) has been reported to be stable or to decrease with time on CAPD,[133,245,247,248] indicating a stable or decreased peritoneal permeability for macromolecules.

However, the interpretation of most studies (and in particular the cross-sectional studies) of peritoneal transport with time may suffer from methodological fallacy in that patients with "inadequate" peritoneal transport will drop out, so that both fast transporters (insufficient fluid removal) and slow transporters (insufficient small solute clearances) may drop out, resulting in selection bias.

Loss of Ultrafiltration Capacity

With time on PD there is an increasing risk of developing loss of UFC, with a markedly higher incidence among patients treated with acetate-containing dialysis solutions.[210,237,246] Using the standard lactate-based solutions, the risk of developing permanent loss of UFC (using a clinical definition) increases markedly with time on CAPD being 9% after 48 months and 35% after 72 months of PD.[237]

There are several pathophysiological mechanisms behind ineffective fluid removal as a result of permanent loss of UFC (Table 26-2). Increased transport of small solutes with rapid glucose absorption is the most common mechanism observed in CAPD patients with impaired UFC.[133,138,139,237,249,250] The rapid glucose absorption results in rapid loss of the osmotic driving force (glucose gradient) and, consequently, a rapid decline in ultrafiltration rate. However, detailed kinetic analyses of patients with UFC as a result of rapid diffusive transport also show that the remaining osmotic gradient cannot induce water flow as effectively as in patients with normal UFC, indicating a decreased osmotic conductance of the peritoneal membrane.[82,251]

TABLE 26-2 Suggested Causes of Ineffective Fluid Removal in CAPD

A. Obstructed outflow and increased residual dialysate volume
B. Loss of residual renal function
C. Subcutaneous or retroperitoneal leakage
D. Loss of ultrafiltration capacity as a result of:
   1. Increased solute transport (most common mechanism)
   2. Reduced osmotic conductance (impaired transcellular water transport or reduced UF coefficient; not uncommon, often combined with 1 in long-term PD patients)
   3. *"Hypopermeable peritoneum"* with decreased water transport or decreased surface area (extremely rare)
   4. Increased peritoneal fluid absorption (probably rare)

A selective decrease in ultrafiltration in patients with normal diffusive glucose transport has also been reported in some CAPD patients (with loss of UFC), who also had a minor decline of dialysis sodium concentration when using hypertonic glucose solution.[139,140,252] This may imply a decreased hydraulic conductivity of the peritoneal membrane, and it was suggested that these alterations may be the result of decreased transcellular water transport (deficient aquaporin-mediated ultrafiltration) and that this may be an additional cause of UFC failure. However, this finding needs to be interpreted with caution because when the ultrafiltration rate is low, a reduction of dialysate sodium caused by the dilution of dialysate by ultrafiltrate will not occur to the same degree. Sodium sieving will always be markedly reduced when ultrafiltration is poor, even when the aquaporin function is normal.[253] An alternative explanation to the normal glucose transport without decline of dialysate sodium could be a combination of selective changes in the peritoneal ultrafiltration coefficient in combination with increased surface area.[19] This would result in unchanged diffusive solute transport in combination with reduced ultrafiltration coefficient across both transcellular water pores (aquaporins) and small pores.[135]

Loss of peritoneal surface area with slow solute transport as a result of fibrosis and the formation of adhesions has been reported during the late stage of EPS in a few cases.[249] However, detailed studies in four patients developing EPS showed increasing PS in three of the patients,[254] suggesting that loss of UFC associated with increased solute transport in these patients was an early sign that preceded the development of more overt signs of EPS. Thus initially EPS seems to be associated with increased peritoneal solute transport, which later is followed by formation of adhesions and finally encapsulation of the intestinal loops, resulting in slow peritoneal solute transfer caused by loss of the surface area.[249] However, slow solute transport seems to be an extremely rare cause of UFC loss, and only a few cases have been reported.

Increased peritoneal fluid absorption has also been reported as the cause of UFC loss.[133,139] The increase in peritoneal fluid absorption in these patients is not due to increased lymphatic absorption but to increased fluid

absorption into the peritoneal interstitial tissue, indicating changes in the interstitial tissue fluid hydraulic conductivity.[62] The mechanisms behind these changes are not clear. Increased fluid absorption may also be caused by subcutaneous or retroperitoneal leakage of the dialysate.[255] Because retroperitoneal dialysate leakage can be diagnosed with only computed tomography, magnetic resonance imaging (MRI) scan, or scintigraphy, it is possible that some cases of increased fluid absorption in fact are due to undiagnosed retroperitoneal leakage.[255]

Relation Between Peritoneal Transport Characteristics and Clinical Outcome

Peritoneal transport characteristics have a major impact on the clinical management and outcome in peritoneal dialysis patients. The patients' peritoneal small solute transport characteristics will have a major impact on the optimal dialysis prescription as regards ultrafiltration and small solute clearances. Furthermore, a high/fast peritoneal transport rate has been identified as an important risk factor for both PD technique failure and mortality.[145,256–261]

Although the reasons for this are not established, several different mechanisms may contribute. At first, there is an association between a fast peritoneal transport rate and comorbidity, including diabetes, cardiovascular disease, and chronic inflammation (with elevated plasma levels of C-reactive protein (CRP) and IL-6).[149,256,262–266] Second, high transporters have a more rapid glucose absorption and, thus an impaired fluid and sodium removal, and have a high risk to chronic fluid overload,[148,259,267–269] which in itself is associated with LVH and LV dysfunction in PD patients[270] and may potentially cause immune activation because of bacterial or endotoxin translocation in patients with severe gut edema as a result of severe volume overload.[271,272] In contrast, although a low fluid removal may result in low urea clearance, peritoneal clearances for larger solutes than urea are usually not lower in fast transporters. During standard CAPD, the Kt/V_{urea} is not different between transport groups, and creatinine clearance is usually higher in high/fast transporters (see Table 26-1).[111,131]

Because there is a close relationship between the peritoneal transport characteristics of solutes of different molecular weight up to the size of albumin (see Figure 26-2),[37,111] it is not surprising that many patients with fast peritoneal transport also exhibit increased protein losses and that these patients have more severe hypoalbuminemia than patients with lower D/P ratios.[257,273,274] It is interesting to note that the low serum albumin levels are already present in high transporters before the initiation of PD,[275] indicating that another mechanism, such as inflammation, may also contribute. Furthermore, a large influx of glucose absorbed from the dialysate may suppress appetite,[257,276] although Davies and colleagues[277] reported that calories derived from the dialysate in CAPD patients did not seem to reduce appetite in PD patients. The low albumin levels and increased glucose absorption in high transporters lead to the hypothesis that a fast transport state will lead to malnutrition, which, in turn, may affect clinical outcome. However, except from low serum albumin levels, high transporters do not seem to be more malnourished as regards other nutritional parameters.[145,274] Furthermore, there were no signs of change in any nutritional parameter in fast transporters in a longitudinal study of nutritional parameters.[278]

It is striking that the relation among peritoneal transport rate and serum albumin[145] and some other nutritional markers was seen already at start of CAPD.[278] Therefore, it is likely that the relation between peritoneal transport and some nutritional parameters seen in some studies, in fact, are due to a relation between peritoneal transport and the malnutrition, inflammation, and atherosclerosis (MIA) syndrome.[279] Fast peritoneal transport characteristics may thus be another feature of the MIA syndrome.[279]

Moreover, it is important to note that the etiology and clinical features of fast transporters may be different. It has recently been suggested that there may be different types of fast transporters[148,280] and that the prognosis may depend on the type of fast transporter.[148–150] Type I is an early inherent type which is associated with increased mortality mainly because it is associated with comorbidity, low residual renal function, and inflammation; these patients would also have a poor prognosis if they were treated by hemodialysis. Type II is an early inherent type with a large peritoneal surface area, and type III is a late acquired type with transport changes that develop with time on PD; the latter two types do not necessarily have higher prevalence of inflammation or comorbidities, such as diabetes mellitus and cardiovascular disease. These patients will have a good prognosis if fluid balance is controlled using automated peritoneal dialysis (APD) and icodextrin-based PD solution.[281] In addition, other patients may perhaps exhibit an increase in transport rate over time on PD because of the development of clinical complications, resulting in increasing inflammation. The relative importance of the different types of fast transporters and their contribution to the poor clinical outcome of high/fast transport patients is not known.

In addition, an increased peritoneal albumin clearance (or large pore flux from the PDC test) has recently been reported as an independent predictor of poor clinical outcome.[282,283] It may, to some extent, be related to inflammation and cardiovascular disease and has, furthermore, been suggested as a marker of endothelial dysfunction.[284]

Changes in Peritoneal Morphology with Time on Peritoneal Dialysis

During the last 15 years, several small studies have demonstrated marked changes in peritoneal morphology in patients treated with PD, including mesothelial denudation, submesothelial thickening and fibrosis, and vascular changes with vascular basement membrane reduplications.[285–288] More recently, fibroblast like cells transdifferentiated from mesothelial cells that has undergone epithelial to mesenchymal transition (EMT),[17,289,290] vascular changes with subendothelial hyalinization and neoangiogenesis,[291–293] and accumulation of advanced glycation end products (AGEs) in the peritoneum[291,294] have been reported, factors which also were related to functional changes with increasing peritoneal solute transport.

The Peritoneal Biopsy Registry reported the analysis of biopsies from the parietal peritoneum in 130 PD patients

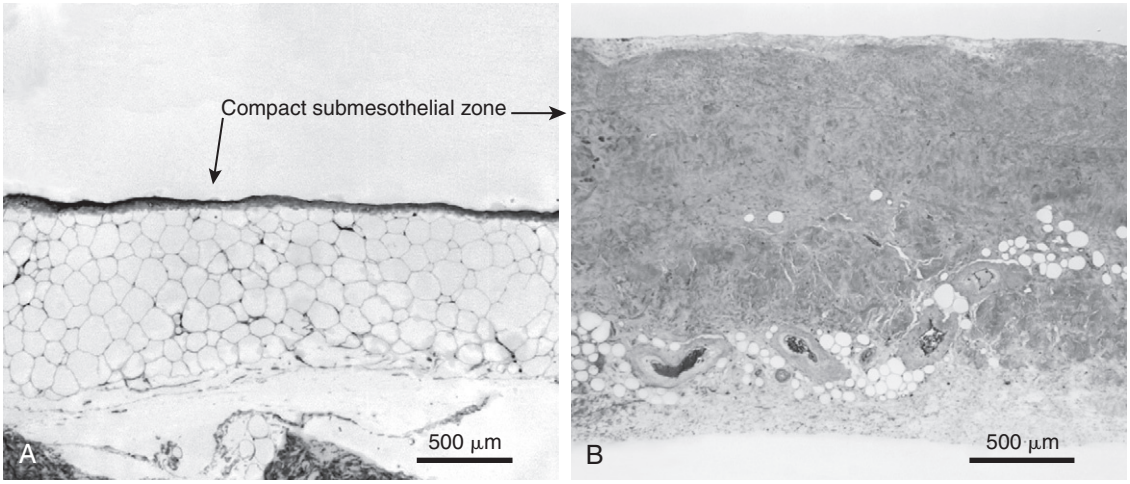


FIGURE 26-5 Parietal peritoneal biopsies from a normal individual (A) and from a patient who had been treated with PD for 9 years (B). Note the marked expansion of the submesothelial compact zone in **B**. (From J.D. Williams, K.D. Craig, N. Topley, et al., Morphological changes in the peritoneal membrane of patients with renal disease, J. Am. Soc. Nephrol. 13 [2002] 470-479.)

and compared them to peritoneal biopsies from normal individuals and uremic subjects not treated with PD.[18] The most dramatic changes were the marked increase in the submesothelial compact zone (which approximately equals the interstitium), which was 50 μm in normal subjects, 150 μm in hemodialysis patients, and 270 μm in PD patients. The thickness increased markedly with time on PD from 180 μm in patients treated with PD for less than 2 years to a median value of 700 μm in patients treated for more than 97 months (Figure 26-5).[18] Vascular changes with progressive subendothelial hyalinization and luminal narrowing or obliteration were seen in 56% of the PD patients and increased with time on PD. Patients with membrane failure had higher submesothelial thickness and also a higher density of blood vessels, which correlated with the degree of fibrosis.[18]

In a few patients that had been treated with PD for several years, progressive peritoneal fibrosis with development of EPS have also been reported. This is a frightening complication with fibrotic thickening of the peritoneal membrane, formation of adhesions, and in the last phase encapsulation of the intestinal loops and formation of an intestinal cocoon.[212]

Pathophysiological Considerations

Potentially Causative Factors

The pathogenetic mechanisms behind the structural and functional alterations in the peritoneal membrane are not clear, but both bioincompatibility of the peritoneal dialysis solutions and the effect of peritonitis have been discussed. Davies and colleagues[239] reported that recurrences or clusters of peritonitis and the cumulative dialysate leukocyte count were related to increased D/P creatinine and reduced UFC, whereas D/P creatinine and UFC were stable in patients with no or single isolated peritonitis episodes. However, the relationship between peritonitis and high solute peritoneal transport rate is not evident in studies of patients with loss of UFC, where most studies have failed to demonstrate any relation between the number of peritonitis episodes and loss of UFC.[133,250] Although numerous studies have demonstrated the bioincompatibility of the presently used peritoneal dialysis solutions in vitro, and bioincompatibility has been extensively discussed as a cause of changes in peritoneal solute transport,[180,295] there are little clinical data demonstrating such a relationship, except from the relation between loss of UFC and the use of acetate as buffer. However, it should be noted that until recently, almost all standard peritoneal dialysis solutions have had similar composition and biocompatibility. Much attention has focused on the relatively high content of reactive carbonyls in the conventional PD solutions.[179,180,296] These reactive carbonyls are particularly of interest because they are more potent promoters of formation of AGEs than glucose itself.[296] The potential pathogenetic role of carbonyls and AGEs in the changes of peritoneal function are supported by the facts that increased AGE content has been found in the peritoneum of long-term PD patients and was furthermore associated with increased peritoneal small solute transport.[291,294] In adition, AGEs may stimulate the transdifferentiation of mesothelial cells to undergo EMT.[17] Also, it has been reported that patients with increasing small solute transport (as assessed from the PET) with time on PD had a higher glucose exposure compared to patients with stable peritoneal membrane transport.[297]

Physiological Mechanisms

The mechanism(s) by which small solute transport increases in patients with poor ultrafiltration and increased small solute transport is not yet understood. It has been suggested that the cause of the increased small solute transport rate is an increase in peritoneal vascular surface area as a result of neoangiogenesis, which has been demonstrated in the peritoneal membrane.[18,158,291–293] However, if this was the only explanation, the protein losses should also be increased among these patients because of the larger vascular surface area. However, it is possible that the markedly expanded interstitium (submesothelial compact zone) retard macromolecular transport more than small solute transport, resulting

in an increased small solute transport and normal macromolecular transport.[19]

In reduced osmotic conductance (reduced osmotic efficiency of glucose) observed in many patients, it has been suggested that this is due to decreased transcellular water transport (deficient aquaporin-mediated ultrafiltration).[139,140,252] However, this is still not established, and the aquaporin expression was, in fact, reported to be normal in a long-term PD patients with poor ultrafiltration attributed to impaired transcellular water transport.[298] Furthermore, computer simulations have demonstrated that sodium sieving will always be markedly reduced when ultrafiltration is poor, even when the aquaporin function is normal.[253] Also, an expanded matrix of fibers coupled in series with the three pore membrane can simulate these changes with reduced osmotic conductance (uncoupling of small solute transport from the peritoneal ultrafiltration coefficient, LpA).[19] Therefore, further research is needed to establish the pathophysiological mechanisms behind the reduced osmotic conductance in many PD patients with poor ultrafiltration.

Devuyst[299] has suggested a model where the increased reactive carbonyls (caused by uremia and the carbonyls in the PD fluid) will amplify the AGE formation in the peritoneal membrane. The carbonyls and AGEs will have several effects, including stimulation of peritoneal cells to produce VEGF. AGEs will also stimulate mesothelial cells to undergo EMT, and transdifferentiated mesothelial cells are an important source of VEGF.[300] The inflammatory response to bacterial peritonitis results in upregulation of several cytokines and growth factors (e.g., TGF-β, IL-1, fibroblast growth factor-2, and angiotensin II) that further stimulate EMT. VEGF will stimulate neoangiogenesis and interact with endothelial cells to produce endothelial nitric oxide synthase (eNOS), which is markedly increased in long-term PD patients[158] and will cause vasodilation and further stimulate neoangiogenesis. Nitric oxide (NO) is a crucial regulator of vascular tone and permeability, and the finding that eNOS knockout mice, to a large extent, were protected against the structural and functional changes induced by acute peritonitis[236] underscores the importance of NO in the pathophysiology of peritoneal membrane dysfunction. The correlation seen between submesothelial fibrosis and neoangiogenesis suggests that these two processes are related,[18,292] and it is likely that transdifferentiated mesothelial cells that have undergone EMT are not only an important source of VEGF,[300] but also play an essential role in the initiation of fibrosis and in the synthesis of matrix components such as collagen I and fibronectin.[17] It is in this context of interest that uremia per se and the binding of VEGF to the extracellular matrix will induce the release of basic fibroblast growth factor (bFGF), which has fibrotic and angiogenetic effects.[299] Furthermore, inflammatory cytokines like IL-6 may also stimulate neoangiogenesis and fibrosis.

However, even if much progress has been made during the last few years, our knowledge is still insufficient about which factors will be most important in causing the long-term changes in the peritoneal membrane structure and function, and about the pathogenetic mechanisms involved in the evolution of these alterations. Much further research is clearly needed in this area.

A full list of references are available at www.expertconsult.com.

Chapter 27

THE UTILIZATION AND OUTCOME OF PERITONEAL DIALYSIS

Yi-Wen Chiu, M.D. and Rajnish Mehrotra, M.D.

Even though peritoneal dialysis (PD) was first performed in humans by Ganter in 1923,[1] the first successful treatment of acute renal failure using "peritoneal irrigation" was described more than 20 years later by Fine, Frank, and Seligman in 1946.[2] The subsequent use of the intermittent PD therapy was limited, however, by the lack of availability of commercial dialysis solutions and the need for repeated abdominal puncture. In 1950, Odel and coworkers[3] reviewed the experience with the first 100 patients treated with intermittent PD, from 1923 to 1948 and concluded that this therapy should be restricted to patients with reversible acute renal failure. With the introduction of Tenckhoff catheter in 1968, and the portable/wearable equilibrium dialysis technique in 1976 (renamed soon after as continuous ambulatory PD [CAPD]), PD became a viable renal replacement therapy for the long-term treatment of patients with end-stage renal disease (ESRD).[4–6] This early experience led to a progressively larger proportion of incident dialysis patients to be treated with PD during the 1980s, further validating its role as an alternative to in-center hemodialysis (HD).

However, starting in the early 1990s, PD take-on for incident dialysis patients has decreased significantly.[7] Even though the worldwide PD patient population continues to increase, use of PD by new patients commencing dialysis therapy is decreasing. At the end of 1997, there were 115,000 patients treated with PD, and they represented 14% of global dialysis patients. By the end of 2004, this number had increased to 149,000 but represented 11% of the world's dialysis population.[8] The number of PD patients in selected countries is summarized in Figure 27-1. It needs to be noted that while Mexico has the largest number of patients treated with PD, reliable estimates for patient count for that country are not available through the United States Renal Data System. The recent trends in PD utilization in different parts of the world are summarized in Figure 27-2. As can be seen, PD take-on has been decreasing in North America, Australia, and New Zealand (see Figure 27–2A). However, except in the United Kingdom, PD utilization has remained largely unchanged in most European countries (see Figure 27-2B).

What deserves mention is that it is the progressive increase in the use of automated PD (APD), rather than that of CAPD, that is fueling the overall increase in the number of PD patients in many parts of the world.[7–10] The increase in the use of APD has largely been driven by lifestyle considerations and has been substantially boosted by the introduction of smaller, portable, volumetric cyclers in the mid-1990s. Thus APD use has increased substantially in the United States, Canada, Australia, and many European countries[9,11,12] It is estimated that at the end of 2004, 30% of PD patients were being treated with APD.[8]

USE OF PERITONEAL DIALYSIS

The proportion of dialysis patients treated with PD varies widely in different parts of the world, ranging from less than 2% to more than 80%.[13] Even within the same country there

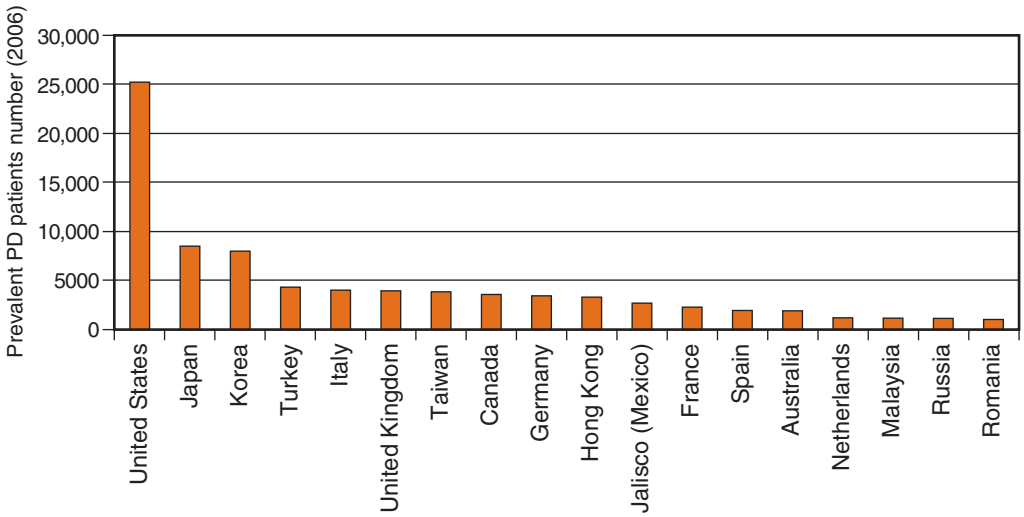


FIGURE 27-1 Estimated numbers of prevalent PD patients, in 2006 in selected countries in different parts of the world. Data used to estimate these numbers were taken from the United States Renal Data System, 2008 Annual Report. It is estimated that Mexico has the largest number of PD patients in the world; however, complete data to estimate the number of patients in that country are not available. (Data from United States Renal Data System, US Department of Public Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD, 2008.)

are large differences in the use of PD as a dialysis modality. For example, in the United States the proportion of prevalent dialysis patients treated with PD ranged from 4.8% in New York to 10.8% in Network 16 (Alaska, Idaho, Montana, Oregon, and Washington) in 2006;[11] in Italy, from 2% to 16% in 2004;[14] and in France, from 2.9% to 26.5% in 2003.[15] A number of factors have been suggested to explain the vast differences in the use of PD in different parts of the world. It is widely agreed that nonmedical factors are substantially more important than medical factors in determining the distribution of dialysis modality in a given unit, region, or country.[16] These nonmedical issues include, but are not limited to, inadequate patient and physician education and healthcare system (including economic considerations) issues. Some of these factors are discussed in the sections below. Similarly, the reasons for the decline in PD take-on in many parts of the world are multifactorial. Given the size of the country's dialysis population, the overall decline in global PD utilization is driven largely by a steep decrease in PD take-on by new patients commencing dialysis therapy in the United States, starting from the mid-1990s.[17]

The decrease in the use of PD might not have been significant had it not been for two important considerations. First, several registry studies (reviewed later) suggest that many subgroups of incident dialysis patients have a survival advantage when treated with PD. Furthermore, over the past decade, the outcomes for PD patients have improved substantially more than for patients undergoing in-center HD.[18,19] Second, there is a strong economic argument for increasing PD utilization.[20] This also is discussed below.

It is for those two reasons that it is important to understand the reasons for the under utilization of PD in many parts of the world. This understanding could possibly lead to the development and implementation of healthcare policies to reverse the declining proportions of dialysis patients beginning treatment with PD.

DETERMINANTS OF USE OF PERITONEAL DIALYSIS

Medical Factors

There are only two absolute contraindications for PD—absence of a functioning peritoneal cavity and lack of a stable home that would allow regular delivery of supplies. A large number of other factors have been considered. However, the relative importance of each of these factors varies from patient to patient and physician to physician.

Frailty often accompanies aging, and this is likely to limit the ability of elderly individuals to undertake a self-care dialysis modality such as PD. Furthermore, many elderly individuals face social isolation, and in-center dialysis may be more appropriate for such individuals. Thus it is not surprising that elderly individuals are less likely to be treated with PD.[11] However, advancing age cannot be considered to be an absolute contraindication to the therapy: it has been successfully performed even beyond the eighth decade of life.[21,22] Aids are available for individuals with limited dexterity or visual acuity that would allow such patients to perform self-care dialysis without an increased risk for touch contamination. PD has also been successfully performed in institutionalized elderly individuals; with adequate training of the nursing home staff, and support of the PD program, the outcomes are similar to those obtained with community dwelling patients.[23] In many healthcare systems (Canada, Denmark, and France), assisted PD has been successfully performed.[24–26] Either a member of the family or a nurse provides in-home support to the patient to perform either CAPD or APD. The medical outcomes with assisted PD are comparable to those achieved with patients who perform their own care. Furthermore, the total costs of assisted PD in these societies are still lower than for in-center HD, and thus the approach is economically feasible. Finally, the experience from Canada suggests that many patients require decreasing level of

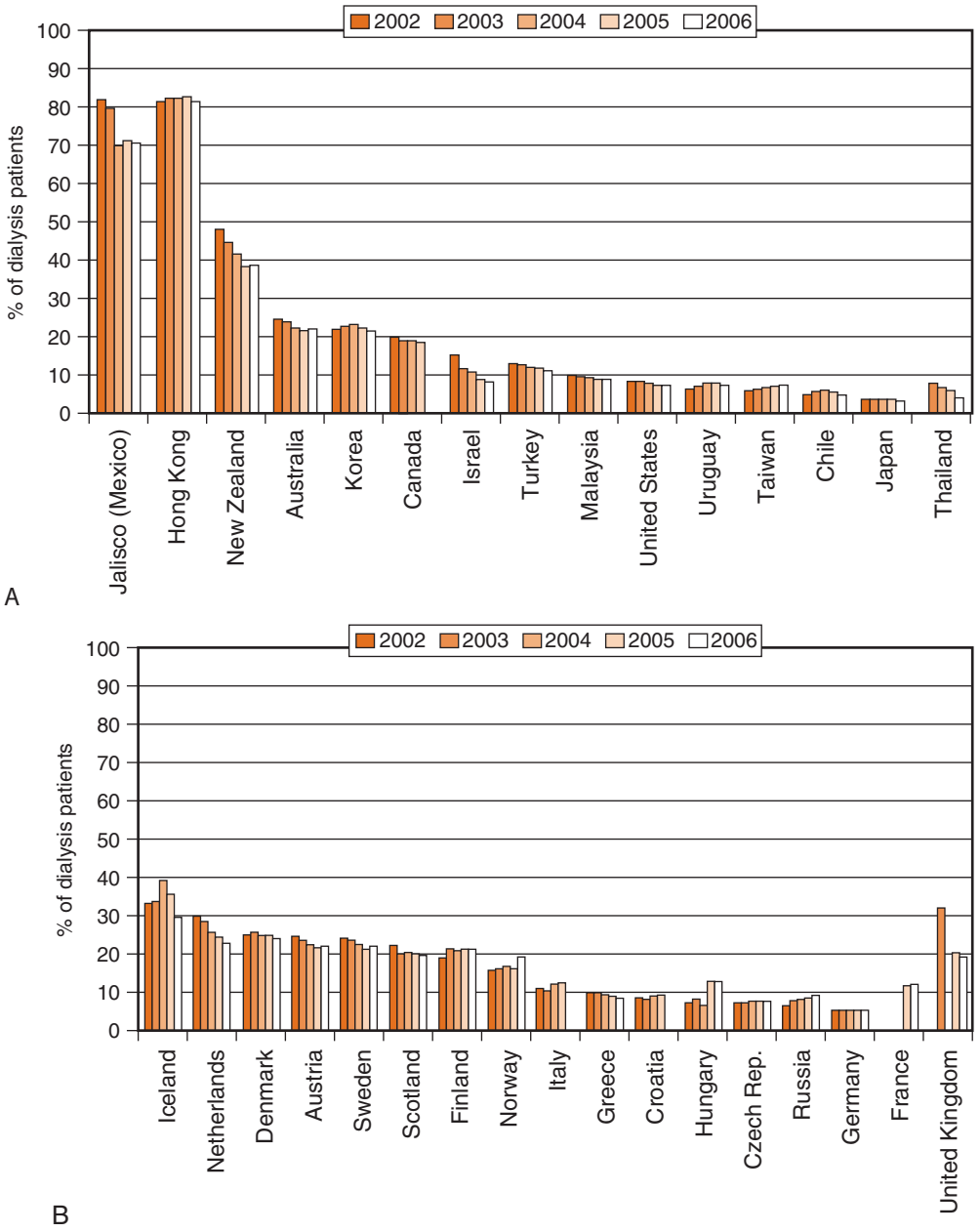


FIGURE 27-2 **A,** Trends in proportion of dialysis patients treated with PD in selected countries or regions in the Americas, Asia, Australia, and New Zealand over the 5-year period, 2002 to 2006. Data are derived from the 2008 Annual Report of the United States Renal Data System. **B,** Trends in proportion of dialysis patients treated with PD in selected European countries over the 5-year period, 2002 to 2006. Data are derived from the 2008 Annual Report of the United States Renal Data System. (Data from United States Renal Data System, US Department of Public Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD, 2008.)

support (with substantially fewer than the 14 allowable weekly visits) and occasionally may be able to perform self-care dialysis independently.[24] These experiences suggest that PD can be successfully performed in the elderly and under several circumstances may be the preferred therapy.

Large body size also is often considered to be a contraindication to PD. However, success of PD depends on whether the large body size is secondary to excessive body fat or large muscle mass. Obesity accounts for the vast majority of large individuals. Fat mass contributes substantially less to the daily nitrogenous load that needs to be removed with dialysis therapy; thus obese individuals are as likely to achieve adequate small solute clearance targets as nonobese individuals.[27] Adequate placement of the exit site for the PD access is probably the biggest impediment to the successful application of PD in the obese individuals. Care should be exercised to prevent the placement of the exit site under the pannus. In many patients, it may be necessary to use catheter extenders to fashion either an upper abdominal or a presternal exit site.[28–30]

Patients who have had a previous abdominal surgery may have adhesions; these may preclude the successful placement or function of a PD catheter. However, many such patients have no adhesions or can undergo successive selective adhesiolysis if the catheter is being placed using laparoscopy.[31,32]

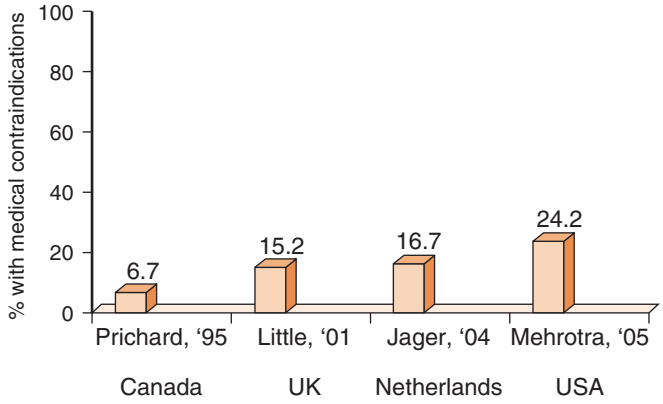


FIGURE 27-3 Proportions of patients with absolute or relative medical contraindications to peritoneal dialysis in different parts of the world. Data collated from references 35 to 38.

In one such series, almost one half of all patients who had a successful placement of PD catheters using advanced laparoscopy had a previous history of abdominal surgery.[31,32] Similarly, PD catheters have been successfully placed and used in patients with previous ostomies;[33,34] a presternal catheter is particularly advantageous in such situations.

Studies from different parts of the world show that more than three quarters of incident dialysis patients have neither an absolute nor a relative contraindication to performing self-care dialysis (Figure 27-3).[35–38] Indeed variability in demographic, clinical, social, and pre-ESRD care account for a quarter or less of the variability in the use of PD in the United States.[39] Moreover, analyses of the USRDS data indicate that changes in age, body size, and comorbidity burden of new dialysis patients over the past decade are small and are clearly insufficient to explain the rather steep decline in PD use in the United States.[18] All these data argue for a strong role for nonmedical factors in the selection of dialysis modality.

Nonmedical Patient Related Factors

The institution of dialysis therapy requires patients to make substantial changes in lifestyle. Consideration of the lifestyle implications of the therapy by the patient and his or her family are often central to the selection of the self-care dialysis modality such as PD. For example, the proportional use of PD is higher in children and young adults (so that they can attend school) or among those who are either seeking employment or want to continue to work.[11] Alternatively, the farther the patient lives from a dialysis unit, greater is the potential lifestyle advantage for a patient to choose to dialyze at home.[39] Indeed, substantially more PD patients report that they played an active part in the selection of their dialysis modality when compared to those who start treatment with in-center HD.[40] However, patient choice may be limited by the availability of different dialysis modalities in a given geographic area; given the long distances from dialysis units, home dialysis could potentially be an attractive therapy for patients living in rural and remote rural areas. Surprisingly, the dialysis units in rural and remote rural areas in the United States are substantially less likely to have the infrastructure to support home dialysis, and use of PD and home HD in these areas is substantially less than in the urban areas.[41]

However, demographic, clinical, and geographic factors explain only about 10% of the variability in the use of in-center HD and PD in the United States.[39] The nature and focus of education of a patient about different dialysis modalities is probably one of the most important factors that explains the highly variable take-on rate for PD.[38] The vast majority of new dialysis patients in the United States are not aware that they could use PD (or home HD or transplantation) as a renal replacement therapy.[38,40] Numerous observational studies have also indicated that patients who undergo predialysis modality education are more likely to select PD for treatment.[35,36,42–44] Finally, in a randomized, controlled trial patients who underwent two-step, predialysis education were more likely to choose to dialyze at home when the time came to begin renal replacement therapy.[45]

Predialysis education is an iterative process and often requires multiple visits. Expert groups recommend that predialysis education should begin when the glomerular filtration rate falls to less than 30 ml/min. Modality education is an important component, albeit only one of many, in predialysis education. Surveys of patients undergoing in-center HD suggest that fear of complications or potential lack of supervision of their treatment at home prevented them for choosing to dialyze at home.[46] Thus in addition to informing patients about their choices of dialysis modalities, the educational program should focus on addressing the concerns and fears of patients about performing dialysis at home. Earlier in the course of their kidney disease the modality education begins and greater the amount of time spent in educating patients, the more likely they are to select PD for their treatment.[38] Conversely, longer the patient has been undergoing a particular dialysis modality, the less likely the patient is to consider an alternative dialysis modality.[47,48]

Nonmedical Healthcare System Factors

The healthcare system factors that determine the utilization of PD operate at national, regional, and local levels. Dialysis therapies are expensive; however, the cost structures for in-center HD and PD are different. In-center HD requires higher initial capital costs, and the manpower costs constitute a large component of the recurring expenses. On the other hand, setting up a PD program has low initial capital costs, but requires ongoing payments for dialysis solutions. The manpower costs are lower than for HD, but costs of disposables constitute a larger share of the total expenses. In developed economies, the manpower costs are much higher, and so it is not surprising that the per-patient costs of in-center HD are higher than for PD. Recognizing this imperative, physicians from the United States, Canada, and United Kingdom seem to concur that more than one third of dialysis patients should undergo home dialysis.[49–51] This also forms the rationale for the "PD-first" policy of the Hong Kong government, where, as long as there are no medical contraindications, all new dialysis patients are expected to begin treatment with PD. Even though a change in dialysis modality is required more often for PD patients than for those undergoing in-center HD, the overall cost to provide care for patients who begin dialysis treatment with PD in the United States is

substantially lower than that of those treated with in-center HD.[52] The cost ratio for CAPD to in-center HD in the United States has been estimated to range between 1.2 and 1.52.[20] The cost advantage of CAPD over in-center HD has been shown in many developed economies including Canada (cost-ratio, 1.56-1.9), France (1.13), Denmark (1.06 to 1.51), Italy (1.19 to 2.4), Netherlands (1.05 to 1.54), Hong Kong (2.39), and Taiwan (1.56).[20] Studies from Canada and Netherlands suggest that costs of CAPD are lower than, or the same, as that of home HD. Albeit limited, cost comparisons of APD to in-center HD also generally favor PD.[20] Thus a greater PD use has the potential to partially relieve the economic pressures from the progressively larger ESRD population.[52–54] On the other hand, in many developing economies, manpower costs are substantially lower, and if there is a need to import dialysis solutions, the per-patient costs of PD are substantially higher than for HD. This explains the relative lower use of PD in Eastern Europe, Latin America, and many Asian countries.[55]

In many European countries, the mechanism for funding the healthcare system is an important determinant of utilization of PD. Thus PD is used significantly more in countries with a "public" funding of the healthcare system compared to those with largely "private" funding.[16,56] In the United States, dialysis units are increasingly owned by large corporations, the so-called large dialysis organizations. Despite similar patient characteristics, use of home dialysis modalities varies significantly across different corporations.[57] These observations in both Europe and the United States suggest that financial considerations and corporate policies have a significant influence on the proportional use of PD for renal replacement therapy. At a regional or local level, proliferation of HD units has been shown to decrease the use of PD.[54]

It has been argued that physician and facility reimbursement may be one of the most important determinants of the choice of PD.[16,54,58] However, financial incentives have not translated into a greater utilization of PD in Canada (province of Ontario), Germany, or the United States.[59,60] Not surprisingly, both physician training in and enthusiasm for PD are important determinants of the relative use of different dialysis therapies.[7,61,62]

OUTCOMES WITH PERITONEAL DIALYSIS

Unquestionably, renal replacement therapies prolong the life of patients with ESRD. Even though a randomized, controlled trial has not been undertaken, several observational studies suggest that patients who receive a renal transplant have a survival advantage when compared to similar waitlisted patients undergoing dialysis therapy.[63] This survival advantage with renal transplantation is apparent even when the kidney is from a "marginal" donor.[63,64] Most people agree that this survival advantage, coupled with substantial improvements in quality of life, makes renal transplantation the modality of choice for medically appropriate patients with ESRD. However, the availability of suitable organ donors is limited, and thus most patients with ESRD require long-term dialysis therapy to survive.[11] To determine if one dialysis modality (in-center HD, or home HD or PD) is associated with a greater longevity either in the entire ESRD population or subgroups, has generated a lot of interest. In this section, the data comparing the outcomes of in-center HD to PD and the outcomes with PD in different subgroups of patients are summarized.

Problems in Comparing Outcome of In-Center Hemodialysis and Peritoneal Dialysis

A randomized, controlled trial is probably the most reliable method to determine if any differences in outcomes of patients treated with in-center HD or PD are attributable to the dialysis modality with which they are treated. However, the lifestyle implications of the two dialysis modalities are very different, and this it makes it very challenging to recruit patients who agree to be randomized to the two different dialysis modalities. The most recent attempt to conduct a randomized, controlled trial to compare the effect of dialysis modality on subjects' quality of life was undertaken under the auspices of Netherlands Cooperative Study of Dialysis (NECOSAD).[65] Of the 773 eligible subjects, 735 had a clear preference for one of the two dialysis modalities and refused to be randomized.[65] This clinical trial enrolled only 38 subjects and thus was substantially underpowered to allow any meaningful conclusions.[65] Even though it is possible that a randomized, controlled comparison of in-center HD and PD will one day be done, it is unlikely to happen in the near future.

In the absence of an adequately powered randomized, controlled trial, one has to depend upon observational studies. There are two major challenges with such studies. First, there are substantial demographic, clinical, and social differences between patients who chose to be treated with in-center HD and PD. Second, the allocation of dialysis modalities in these studies is nonrandom. Thus even with the use of innovative statistical techniques, it is often difficult to determine if the differences in outcomes reported by such observational studies are truly attributable to the dialysis modality.

Despite the recognition of the above-mentioned challenges and limitations, the history of intermodality comparisons is replete with examples of inappropriate statistical adjustment. This, in turn, has often led to apparently disparate results using the same datasets.[66–69] This is discussed in more detail in the next section. Furthermore, if a patient changes the dialysis modality over time, the outcomes (e.g., death) could be attributed to the current therapy rather than the one the patient started treatment with at the onset of the ESRD (as-treated analysis vs. intent-to-treat analysis). Both as-treated and intent-to-treat analyses have their advantages and disadvantages, and it is probably appropriate to consider both methods in looking at outcomes. When using the as-treated analysis, it is important to allow for a grace period such that the deaths that occur during a predefined interval after the change in dialysis modality (usually 45-60 days) are attributed to the previous rather than the current therapy. These are just a few examples of the known complex, technical considerations when interpreting the results of intermodality comparisons. It is for these additional reasons that it remains unclear if any of the observed differences in outcomes in patients treated with different dialysis modalities are indeed attributable to the therapy.

Studies Comparing Risk for Death for In-Center Hemodialysis and Peritoneal Dialysis

Ever since the introduction of CAPD for the long-term treatment of patients with ESRD, researchers have been interested in determining if the two dialysis modalities—in-center HD, and PD—provide equivalent outcomes. The comparisons conducted during the 1980s included relatively small number of patients treated in a single center. However, many studies with large patient populations have been conducted. These studies fall into two broad categories: registry-based studies or prospective cohort studies. Studies that use data from existing national or regional registries are particularly attractive since the additional cost of performing the analyses is relatively small. Moreover, they include data on virtually all patients undergoing dialysis therapy in the country or region and thus provide external validity to their findings. However, they are limited by the amount of information available about each subject. As a result of this lack of detail, it remains unclear if differences in outcomes are attributable to the modality or to some differences that remain unaccounted for in the analyses (residual confounding). Prospective cohort studies overcome this limitation since they are designed to collect detailed baseline and follow-up data for each subject. However, they are expensive to conduct, and hence the sample sizes for these studies generally are only a fraction of those for the registry studies.

The data from the key studies using registry data from different parts of the world are summarized in Table 27-1[66–81] and from prospective, cohort studies in Table 27-2.[82–89] Even though the results appear disparate, a close inspection of the results of the studies allows one to make a few general conclusions. First, intermodality comparisons are complex and are not amenable to generalizations. Second, the relative risk (RR) for death among patients treated with HD and PD changes over time. The early intermodality comparisons did not recognize the change in RR over time, and enrolled any or all patients undergoing dialysis at a given point in time ("prevalent" cohort).[66] This, in turn, yielded misleading information. Thus studies that seek to compare the outcomes of patients treated with two different modalities should begin observation at the time when patients first start dialysis therapy ("incident" cohort). Studies of incident cohorts yield a remarkably consistent conclusion: most such studies indicate that treatment with PD is associated with a survival advantage. The length of time over which this survival advantage persists (1-5 years) varies in studies from different parts of the world and also varies in patient subgroups as discussed later.

Third, the RR for death for patients undergoing PD, compared to those treated with in-center HD, depends on the presence or absence of some clinical factors. In this context, three clinical factors are known to influence the RR: age, diabetic status, and other coexisting medical conditions (statistically significant interactions).[69] Studies that failed to take into account the modifying effect of age, diabetic status, and comorbidity have also yielded misleading information.[67,68] On the other hand, studies that have taken these interactions into account allow us to make the following broad conclusions: the better the overall health of a patient, the greater and longer the survival advantage for patients starting treatment with PD.[69] Thus most studies indicate a robust survival advantage with PD for nondiabetics and younger diabetics with no other coexisting medical conditions. Conversely, the poorer the overall health of a patient, the lesser and shorter the survival advantage with PD. Indeed, in some subgroups of these patients (such as older diabetics), the risk for death among those treated with PD is higher than for those treated with HD.

Fourth, most of the studies from North America included patients who started dialysis prior to 2000. Analyses of data from the United States Renal Data System indicate that over an 8 year period, from 1996 to 2004, there have been substantial improvements in both short-term and long-term outcomes of new patients starting treatment with PD.[18,19] On the other hand, there have been no improvements in the 1-year outcomes of patients starting treatment with in-center HD.[18] These discrepant changes in outcomes for patients treated with the two dialysis modalities argue strongly against extrapolating the studies conducted on patients who started dialysis therapy in the 1990s to the present day. Instead, the relative outcomes with the two dialysis modalities should be reevaluated in contemporary cohorts. In contrast to the greater improvements in outcomes of PD patients in North America over the past decade, analyses of data from the registry in Australia and New Zealand (which includes patients who started treatment up to 2005) indicates a shorter-lived survival advantage with PD.[81] These discrepant observations make an even stronger case for such reevaluation in different parts of the world.

Notwithstanding the overall consistency of the observations in the older cohorts, neither the registry studies nor the prospective cohort studies allow us to attribute causality. It remains unclear if any of these differences are attributable to the modality or to the differences in the characteristics of the patients who chose the given dialysis modality. Furthermore, the statistically significant differences in complex statistical models translate into 2 to 4 months of difference in life expectancy.[69] It then appears reasonable to suggest that rather than to allow the results of these intermodality differences to dictate clinical practice, patients should be given the opportunity to choose which dialysis modality will best fit with the lifestyle that they desire.

Do Dialysis Modalities have Disparate Biological Effects that Could Explain the Survival Differences?

Dialysis modalities have disparate biological effects, and it is possible that the differential risk seen in different patient populations is secondary to the different biological effects of the two dialysis modalities. Three issues need to be addressed in this regard: the initial survival advantage seen with PD in most cohorts and subgroups; the loss of this survival advantage over time; and the differential improvement in outcomes with the two modalities over time. Understanding these differences would allow providers to identify potential targets for further improvement in outcomes of patients with ESRD.

The apparent initial survival advantage with PD may be a result of either a higher risk for death with in-center HD or

TABLE 27-1 Registry Studies Comparing the Survival of In-Center Hemodialysis and Peritoneal Dialysis Patients

FIRST AUTHOR (PUBLICATION YEAR)	COHORT PERIOD/ COUNTRY	DATABASE	INCLUSION CRITERIA/ SAMPLE SIZE	DATA ADJUSTED FOR:	FOLLOW-UP DURATION	KEY RESULTS
Gentil[70] (1991)	1984-1988 Spain	Andalusian Renal Patients Registry	Incident patients 1104 (HD 842 vs. PD 272)	Age, diabetic status, cardio-vascular disease, entry year, previous IPD	Up to 3 years	No difference in the 3-year adjusted survival rates
Nelson[71] (1992)	1980-1989 U.S.	Michigan Kidney Registry	Incident patients 20-59 years of age; modality defined as one on day 120 of ESRD 4288 (HD 71% vs. PD 29%)	Age, gender, race, year of first ESRD	Mean, 21 months	PD associated with survival advantage for diabetic patients in ITT analyses only, and for patients with glomerulonephritis is AT analyses only
Held[72] (1994)	1986-1987 U.S.	United States Renal Data System (USRDS)[6]	Incident patients; modality defined as one on day 30 of ESRD 4057 (HD 3376 vs. CAPD 681)	Age, gender, race, selected comorbidity, serum albumin, systolic blood pressure	2.25 to 4.25 years	Similar risk for death in nondiabetics; PD with higher risk for death in older diabetic patients
Bloembergen[66] (1995)	1987-1989 U.S.	USRDS	All prevalent patients who survived at least 90 days on dialysis; modality defined on Jan. 1 of calendar year 170,700 patient years, 87.1% treated with HD	Age, gender, race, cause of ESRD, dialysis vintage	Up to 1 year	PD patients had a 19% higher adjusted mortality risk; risk higher in those older than 55 years of age, diabetic patients, females, and dialysis vintage longer than 1 year
Fenton[73] (1997)	1990-1994 Canada	Canadian Organ Replacement Register	Incident patients; modality defined as one on day 90 of ESRD 10,633 (HD 7792 vs. PD 2481)	Age, primary renal diagnosis, center size, follow-up time and selected comorbidity	Up to 5 years	Using AT analyses, PD patients had a 27% lower adjusted mortality risk; survival advantage seen in every subgroup except older diabetic patients (similar survival as with HD in that sub-group), and for the first 2 years
Schaubel[74] (1998)	1990-1995 Canada	Canadian Organ Replacement Register	Incident patients; modality defined as one on day 90 of ESRD 14,483 (breakdown by modality not provided)	Age, primary renal diagnosis, center size, follow-up time and selected comorbidity	Up to 5 years	Using AT analyses, PD patients had a 27% lower adjusted mortality risk; survival advantage seen in every subgroup except older diabetic patients (similar survival as with HD in that subgroup) and for the first 2 years
Vonesh[75] (1999)	1987-1993 U.S.	USRDS	Both incident and prevalent patients; modality defined as one on day 90 of ESRD	Age, gender, race, cause of ESRD	Up to 3 years	No significant differences in risk for death in nondiabetic patients; survival advantage with PD in diabetic patients younger than 50 yrs of age, but higher risk among diabetic patients older than 50 years of age
Collins[76] (1999)	1994-1996 U.S.	USRDS	Incident patients who survived at least 90 days; modality assigned as one on day 90 of ESRD 117,158 (HD 99,048 vs. PD 18,110)	Age, gender, race, cause of ESRD	Through 6/30/ 97	Survival advantage with PD in all subgroups except for older (> 55 years) diabetic females in whom the risk for death was higher with the therapy

Continued

TABLE 27-1 Registry Studies Comparing the Survival of In-Center Hemodialysis and Peritoneal Dialysis Patients—cont'd

FIRST AUTHOR (PUBLICATION YEAR)	COHORT PERIOD/ COUNTRY	DATABASE	INCLUSION CRITERIA/ SAMPLE SIZE	DATA ADJUSTED FOR:	FOLLOW-UP DURATION	KEY RESULTS
Xue[77] (2002)	1995-1997 U.S.	USRDS	Incident patients; dialysis modality defined as one on day on 91 of ESRD 112,077 (HD 96,662 vs. PD 15,415)	Age, gender, race, cause of ESRD, incidence year, body mass index, and selected comorbidity, and laboratory values	Up to 1 year	Nondiabetic patients had a 12% lower death risk with PD; diabetic patients had a 13% higher risk of death with PD
Heaf [78] (2002)	1990-1999 Denmark	Danish Terminal Uremia Register	Incident patients 4921 (HD 3281 vs. PD 1640)	Age, gender, renal diagnosis, and selected comorbidity	Up to 10 years	PD patients had 14% lower risk for death on ITT and 35% lower risk on AT analysis; difference confined to first 2 years; survival advantage seen in all subgroups except for diabetic patients on ITT analysis
Ganesh[67] (2003)	1995-1997 U.S.	USRDS	Incident patients; dialysis modality defined as one on day 90 of ESRD 107,922 (HD 93,900 vs. PD 14,022)	Age, gender, race, cause of ESRD, body mass index, and selected comorbidity, and laboratory values	Up to 2 years	Treatment with PD associated with higher risk for death in all diabetic patients and nondiabetic patients with coronary artery disease; no significant risk for death in nondiabetic patients without coronary artery disease
Stack[68] (2003)	1995-1997 U.S.	USRDS	Incident patients; dialysis modality defined as one on day 90 of ESRD 107,922 (HD 93,900 vs. PD 14,022)	Age, gender, race, cause of ESRD, body mass index, selected comorbidity, and laboratory values	Up to 2 years	Treatment with PD associated with higher risk for death in all diabetic patients and nondiabetic patients with congestive heart failure; no significant risk for death in nondiabetic patients without congestive heart failure
Vonesh[69] (2004)	1995-2000 U.S.	USRDS	Incident patients; dialysis modality defined as one on day 90 of ESRD 398,940 (HD 352,706 vs. PD 46,234)	Age, gender, race, cause of ESRD, body mass index, selected comorbidity, and laboratory values	Up to 3 Years	Among individuals with no comorbidity, lower risk for death with PD in nondiabetic patients, and young diabetic patients; higher risk for death with PD in older diabetic patients irrespective of comorbidity. Among individuals with baseline comorbidity, no difference in risk for death among nondiabetic patients, or younger diabetic patients
Liem[79] (2007)	1987-2002 The Netherlands	Dutch End-Stage Renal Disease Registry	Incident patients; dialysis modality defined as one on day 91 of ESRD 16,643 (HD 10,841 vs. PD 5802)	Age, gender, renal diagnosis, year of first RRT and dialysis center	Up to 16 years	Lower risk for death in patients treated with PD up to 15 months; advantage diminished with increasing age and in diabetic patients; after 15 months, similar risk for death except in elderly, particularly diabetic patients
Huang[80] (2008)	1995-2002 Taiwan	Taiwan Renal registry	Incident patients who survived at least 90 days on dialysis 48,629 (HD 45,820 vs. PD 2809)	Age, gender, selected comorbidity, and diabetic status	Up to 6 years	Overall similar risk for death with two therapies; subgroup studies showed higher risk for death among diabetic patients and those older than 55 years of age
McDonald[81] (2009)	1991-2005 Australia and New Zealand	ANZDATA registry	Incident patients who survived at least 90 days 25,287 (HD 14,733 vs. PD 10,554)	Age, gender, race, body mass index, selected comorbidity, and propensity scores	Up to 12/31/05	Overall 11% lower risk for death in patients treated with PD in the first year, but 33% higher risk after the first 12 months; early survival advantage with PD seen only in young patients without comorbidities

AT, as treated; *ANZDATA,* Australia and New Zealand Dialysis and Transplant; *CAPD,* continuous ambulatory peritoneal dialysis; *ESRD,* end-stage renal disease; *HD,* hemodialysis; *IPD,* intermittent peritoneal dialysis; *ITT,* intent to treat; *PD,* peritoneal dialysis; *RRT,* renal replacement therapy; *USRDS,* United States Renal Disease System.

TABLE 27-2 Multicenter Prospective Studies Comparing the Survival of In-Center Hemodialysis and Peritoneal Dialysis Patients

FIRST AUTHOR (PUBLICATION YEAR)	COHORT PERIOD/ COUNTRY	NUMBER OF CENTERS	INCLUSION CRITERIA/ SAMPLE SIZE	ADJUSTED FACTORS	FOLLOW-UP DURATION	RESULT
Serkes[82] (1990)	1981-1983 U.S.	24	Incident patients 657 (HD 332 vs. PD 325)	Age, gender, race, renal diagnosis, selected comorbidity	Through 1985	No difference in risk for death in either diabetic or nondiabetic patients
Maiorca[83] (1991)	1981-1987 Italy	6	Incident patients 853 (HD 373 vs. PD 480)	Age, gender, renal diagnosis, selected comorbidity	Up to 7 years	No difference in risk for death
Lupo[84] (1992)	1985-1989 Italy	19	Incident patients 1622 (HD 962 vs. PD 660)	Age, gender, selected comorbidity	Up to 6 years	No difference in risk for death
Foley[85] (1998)	1982-1991 U.S.	3	Incident patients; modality defined as one used on day 90 of ESRD 433 (HD 248 vs. PD 185)	Age, gender, selected comorbidity	Mean 41 months	No difference of risk for death, between HD and PD in the first 2 years; thereafter PD patients had a 57% higher risk for death
Murphy[86] (2000)	1993-1994 Canada	11	Incident patients 822 (HD 540 vs. PD 282)	Age, gender, diabetes, acuity of renal failure and selected comorbidity	Mean 24 months	No difference in risk for death
Termorshuizen[87] (2003)	1997-2002 The Netherlands	Netherlands Cooperative Study on the Adequacy of Dialysis	Incident patients; modality defined as one on day 90 of ESRD 1222 (HD 742 vs. PD 480)	Ag, gender, cause of ESRD, Davies comorbidity index, SGA score and laboratory values	Through 2002	No difference in, risk for death during the first 2 years; thereafter higher risk for death for PD patients, particularly among those 60 years of age or older
Jaar[88] (2005)	1995-1998 U.S.	81	Incident patients 1041 (HD 767 vs. PD 274)	Age, gender, race, cause of ESRD, case-mix profile, laboratory values, propensity score and clinic	Up to 7 years	No difference in risk for death during the first year; higher risk for death in the second year for patients treated with PD
Sanabria[89] (2008)	2001-2003 Colombia	13	Incident patients who survived at least 90 days on dialysis 923 (HD 437 vs. PD 486)	Age, gender, socioeconomic status, education, medical insurance, SGA score, selected comorbidity, laboratory variables, cause of ESRD	Up to Dec. 2005	No difference in adjusted mortality rates between HD and PD

ESRD, end-stage renal disease; *HD,* hemodialysis; *PD,* peritoneal dialysis, *SGA,* subjective global assessment.

a lower risk for death with PD. In most populations, the HD patients are older and sicker than the patients who chose a self-care dialysis modality like PD. Even though the statistical models purportedly adjust for these differences in patient characteristics, the adjustment is likely to be incomplete, it often does not account for differences in the severity of the known medical conditions or for the unknown modifiers of outcomes. Furthermore, the risk for infection—particularly access-related infection—is significantly higher in HD patients than those undergoing PD.[90] HD access-related infection occurs most often in patients with a dialysis catheter and is often an intravascular infection. There are data that suggest that acute infections in dialysis patients increase the long-term cardiovascular risk for dialysis patients.[91] Since more than two thirds of HD patients in the United States begin dialysis therapy with a venous catheter, rather than a permanent vascular access, it is conceivable that the higher initial infectious risk translates into a higher overall risk for death in HD patients.[92]

It also is conceivable that the apparent initial survival advantage with PD is, at least in part, a result of the salutary effects of peritoneal dialysis itself. Several observational studies have shown a significantly better preservation of residual renal function in patients treated with PD compared to those treated with in-center HD.[93–97] Only one study was unable to demonstrate a difference in the rate of loss of residual renal function between in-center HD and PD patients; the HD patients enrolled in this study were treated with biocompatible membranes and ultrapure water.[96] While the former is now widespread, the latter is rarely used. Even though the effect of residual renal function is more widely studied in PD patients, it is an important predictor of survival for HD patients as well.[98–103] In the reanalysis of the Canada-United States (CANUSA) study, for every 5 L/week/1.73 m^2 higher mean renal urea and creatinine clearances, the risk for death of PD patients was 12% lower.[102] Similarly, every 1 unit higher residual renal Kt/V_{urea} (K is the rate of clearance, t is the amount of time, and V is the urea distribution volume) was associated with 66% lower adjusted hazard for death in in-center HD patients over a follow-up period of 1.7 years.[103] These data suggest that residual renal function is an important predictor of mortality for dialysis patients, irrespective of treatment modality and the better preservation of residual renal function with PD, may contribute to the early survival advantage seen with this therapy.

Many studies have shown that the survival advantage with PD diminishes over time, and in some subgroups of patients, the risk for death is higher for patients who continue to be treated with PD.[69] Again, the reasons underlying the loss of this survival advantage are not clear, but several potential explanations can be postulated. In most intermodality comparisons, if patients receives kidney transplants, they are excluded from the analyses from that point forward. At least in the United States, the transplantation rate for PD patients is more than twice as high as that for patients undergoing in-center HD.[18] It follows then that the healthiest patients are removed from the PD cohort at a substantially faster rate than from the in-center HD cohort, and this may lead to an apparent loss of survival advantage. However, unique problems can develop in patients treated with long-term PD that may lead to the loss of this survival advantage. There

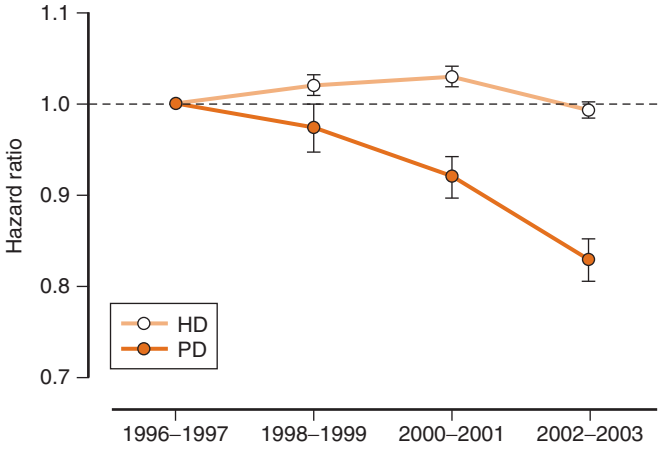


FIGURE 27-4 Over an 8-year period, the outcomes (death or transfer to the other dialysis modality in the first 12 months) improved significantly for new dialysis patients starting PD in the United States, but not for patients starting HD. Using 1996 to 1997 as the reference period and adjusting for demographics, case-mix, and laboratory data, the hazard ratio for death or transfer to the other dialysis modality for patients starting PD in the 2002 to 2003 period was 0.83 (0.79, 0.87) and for patients starting HD in the 2002 to 2003 period was 0.99 (0.98, 1.01). Reprinted from reference 17 with permission.

are several studies that have indicated that with increasing dialysis vintage, PD patients are more likely to become volume overloaded.[104,105] This may occur both as a result of loss of residual renal function and reduced peritoneal ultrafiltration capacity.[106] The latter is thought to occur from the high concentrations of glucose and glucose degradation products generated from heat sterilization of PD fluids.[107] The ensuing volume overload might contribute to hypertension and left ventricular hypertrophy and may further increase cardiovascular risk. Finally, continuous exposure to high-glucose PD solutions may lead to weight gain (generally fat), dyslipidemia, insulin resistance, hyperglycemia, and hyperleptinemia.[108,109]

Finally, studies have shown a differential change in risk for death over the past decade among in-center HD and PD patients in the United States (Figure 27-4).[18] This may be secondary to a more selective assignment of patients to PD, longer transplant waiting times leading to longer retention of healthier patients on PD, reduced infectious risk for PD patients, and a higher a infectious risk for HD patients (with increase in use of tunneled venous catheters).

These considerations allow providers to identify interventions that may potentially reduce the high risk for death in ESRD patients—preservation of residual renal function, reduced use of tunneled venous catheters, and careful prescription management to prevent volume overload and better metabolic control in PD patients.

COMPARISON OF OUTCOMES, OTHER THAN MORTALITY, BETWEEN PATIENTS TREATED WITH IN-CENTER HEMODIALYSIS AND PERITONAL DIALYSIS

In contrast to the controversies surrounding the survival differences, there is general consensus that the HD and PD therapies provide similar health-related quality of life, and PD patients report a higher level of satisfaction with their

care but have a higher probability of transfer to another dialysis therapy (technique failure).[110]

Many, though not all, studies suggest that health-related quality of life for new patients starting either in-center HD or PD are equivalent but impaired when compared to the general population.[111–115] Predictably, quality-of-life scores are worse in patients with a higher number of additional coexisting conditions, a lower hemoglobin level, or residual renal function.[116] With increasing dialysis vintage, while the mental component of the health-related quality of life remains stable, there occurs a deterioration in the physical component of the quality-of-life measure;[115,117] however, these findings have not been consistent across studies.[114] Recent studies suggest that patients treated with PD and nocturnal home HD also report a similar health-related quality of life.[118] Health-related quality of life is a subjective measure, considered from a patient's perspective; the largely equivalent outcomes with the two therapies are reassuring.

Satisfaction with therapy appears to be higher in patients undergoing PD, rather than in-center HD.[47,119,120] This higher satisfaction is probably not a result of the modality itself, but secondary to the education and support provided to patients who participated in the selection of a home dialysis modality. Thus domains in which patients undergoing PD report a higher level of satisfaction pertain to the information provided to them to choose the dialysis modality and the education and support provided by the staff.[47,119]

Finally, PD patients are more likely to transfer to HD, rather than the other way around. The term *technique failure* is often used to describe the event wherein patient changes dialysis modality. The technique failure rate varies from country to country and from area to area.[65,70,83,121–123] Several studies, many done recently, have consistently demonstrated an inverse relationship between PD patient census in a dialysis unit with risk for transfer to HD; thus larger the number of patients in a dialysis unit treated with PD, lower is the technique failure rate (Table 27-3).[19,124–127] The better outcomes observed in larger units are understandable when one considers the reasons underlying the transfer of PD patients to HD: despite great improvements, infectious complication still remain the most common cause for transfer of PD patients to HD, followed by catheter-related problems.[128–132] It is likely then larger units have perfected the system practices that minimize the occurrence of largely preventable causes of transfer of PD patients to HD. Finally, in parallel to reduced risk for death, substantial improvements have been noted in technique survival of PD patients in the United States: for patients who started treatment in the 2002 to 2004 period, the risk for transfer to HD was 38% lower, when compared to those who started treatment in the 1996 to 1998 period[19] (Figure 27-5). This may be secondary to reduction in risk for peritonitis, implementation of continuous quality improvement programs, more selective assignment of patients to PD, or some combination of those factors.

DO CONTINUOUS AMBULATORY PERITONEAL DIALYSIS AND AUTOMATED PERITONEAL DIALYSIS PROVIDE EQUIVALENT OUTCOMES?

As discussed earlier, progressively larger proportion of PD patients are treated with APD, rather than CAPD, particularly in North America and Western Europe.[133,134] There

TABLE 27-3 Effect of Dialysis Center Characteristics on Selected Patient Outcomes

FIRST AUTHOR (PUBLICATION YEAR)	COHORT PERIOD/ COUNTRY	SAMPLE SIZE	MEASURE OF DIALYSIS CENTER CHARACTERSTIC	KEY FINDINGS	
				PATIENT SURVIVAL	TECHNIQUE SURVIVAL
Schaubel[124] (2001)	1981-1997 Canada	17,900 from all Canadian centers	Cumulative patient numbers treated; % of patients starting treatment with PD	Progressively better survival for patients with greater cumulative number of PD patients treated (ref. ≤ 99 patients)	Progressively greater risk of transfer to HD with lower % of new patients starting treatment with PD (ref. ≥ 60%)
Huisman[125] (2002)	1994-1999 The Netherlands	Uncertain/all patients treated in 43 centers	Number and proportion of dialysis patients treated with PD	No relationship	Inverse relationship between unit size and transfer to HD
Mujais[131] (2006)	2000-2003 U.S.	40,869 incident patients in 1768 centers	Number of patients treated with PD	No relationship	Progressive lower risk of transfer to HD with higher PD census
Mehrotra[19] (2009)	1996-2004 U.S.	66,381 incident patients	Period prevalent unit census	No significant trend noted	Progressively lower risk of transfer to HD with higher period prevalent PD census (RR 0.78 for units with > 25 patients, ref. 1-4 patients)
Plantinga[126] (2009)	1995-1998 U.S.	236 new PD patients from 26 clinics	Clinics > 50 patients (Ref. ≤ 50 patients)	No relationship	87% lower risk of transfer to HD in clinics with > 50 pts
Afolalu[127] (2009)	2001-2005 U.S.	5003 incident PD patients from all centers in Network 1	Clinics > 25 patients (Ref. ≤ 25 patients)	No relationship	Significantly higher risk of transfer to HD for smaller clinics in both year 1 and 2 of treatment

HD, hemodialysis, *PD,* peritoneal dialysis, *RR,* relative risk.

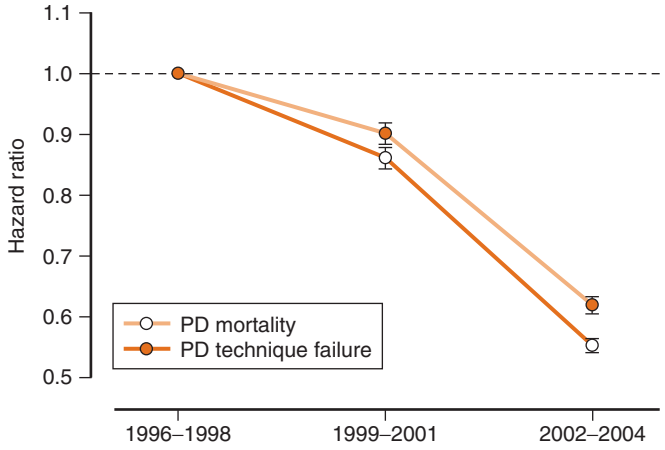


FIGURE 27-5 Compared to new dialysis patients who started PD treatment in the United States in the 1996 to 1998 period, those starting in the 2002 to 2004 period had a significantly lower risk for death or transfer to hemodialysis. The adjusted hazard ratios for death or technique failure for incident patients in 2002 to 2004 were 0.55 (0.53, 0.57) and 0.62 (0.59, 0.64) respectively.

are potential advantages and risks with the use of APD. Early in the course of development of PD, fewer connections and disconnections in patients undergoing APD were associated with a lower risk for peritonitis.[135] However, it is unclear if these advantages persist in the contemporary practice of PD; CAPD patients use twin bags that have substantially reduced the daily number of connections and disconnections patients have to make. On the other hand, studies have raised concern that APD is associated with a lower total removal of sodium and water (with attendant risk for volume overload).[136–138] However, APD prescriptions that limit the number of nighttime exchanges and avoid long dwells with glucose based solutions—with either a partially dry day or use of icodextrin—result in similar volume control as seen in CAPD patients.[139,140] Some studies have raised concern that patients treated with APD lose residual renal function faster than those treated with CAPD.[137,141–144] However, studies regarding loss of residual renal function are inconsistent, and patients in these studies were often not treated with blockers of the renin-angiotensin-aldosterone system (now considered to be the standard of care).[95,97,145,146]

Several studies have compared the "hard" outcomes of mortality and technique survival for patients treated with CAPD and APD. Two randomized, controlled trials have been completed and they were unable to show any differences in the risk for death or transfer to HD.[147,148] However, these trials had small sample sizes and were underpowered to detect a difference. Recently, several large observational studies have been completed and the preponderance of evidence suggests that both the modalities of PD offer similar outcomes (Table 27-4).[10,19,131,149,150] These data suggest that CAPD and APD, as practiced today in different parts of the world, offer similar outcomes. The increasing use of APD in many parts of the world is likely to continue, as it is driven primarily by lifestyle choices made by the patients.

A full list of references are available at www.expertconsult.com.

TABLE 27-4 Summary of Observational Studies that have Compared the Outcomes of Patients Undergoing Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis

FIRST AUTHOR (PUBLICATION YEAR)	COHORT PERIOD/ COUNTRY	DATA SOURCE	SAMPLE SIZE (CAPD VS. APD)	FOLLOW-UP DURATION	OUTCOMES COMPARISON BETWEEN CAPD AND APD	
					PATIENT SURVIVAL	TECHNIQUE SURVIVAL
Mujais[131] (2006)	2000-2003 U.S.	Baxter Healthcare Corporation On-Call system	Total 40,869	Through June 2005	No difference	Better in APD group
Badve[10] (2008)	1999-2004 Australia and New Zealand	ANZDATA Registry	2393 vs. 1735	Though March 2004	No difference	No difference
Sanchez[149] (2008)	2003-2005 Mexico	Single center	139 vs. 98	Through Dec. 2005	Better in APD group	Better in APD group
Mehrotra[19] (2009)	1996-2004 U.S.	USRDS	42,942 vs. 23,439	Through Sept. 2006	No difference	No difference
Michels[150] (2009)	1997-2006 The Netherlands	NECOSAD	562 vs. 87	Through Aug. 2007	No difference	No difference

APD, automated peritoneal dialysis; *ANZDATA*, Australia and New Zealand Dialysis and Transplant; *CAPD*, continuous ambulatory peritoneal dialysis; *NECOSAD*, The Netherlands Cooperative Study on the Adequacy of Dialysis; *USRDS*, United States Renal Disease System.

Chapter 28

PERITONEAL DIALYSIS SOLUTIONS

Simon J. Davies, M.D.

The last 15 years has seen an encouraging trend in the development of peritoneal dialysis (PD) solutions. As our understanding of how the peritoneal membrane works and how this changes with time on therapy is combined with a clearer view of the issues that face patients requiring renal replacement therapy, new solutions have been devised to address these problems.

What are the characteristics of the ideal peritoneal dialysis solution? At the very least it must do the job of dialysis treatment. This includes the removal of water-soluble toxins, maintenance of electrolyte and acid base status, and the removal of salt and water. This in itself might not be so simple. For example, the physiology of the peritoneal membrane turns out to be more complex than originally thought, with different pathways and mechanisms for solute and water removal, respectively. As a result, the ability to create both osmotic gradients with small osmolytes and oncotic gradients with larger, potentially charged molecules is desirable. Given the chance, however, the clinician would like to do more. Solution development opens up the opportunity for therapy—for example, not just maintenance of electrolyte balance but its very manipulation such that, especially in combination with other drug treatments, specific problems associated with renal failure might be treated. Indeed, the peritoneal cavity offers an alternative method of drug delivery that is already being exploited in nonrenal failure patients.[1]

It is also important that solutions used in peritoneal dialysis do no harm to the patient. The literature now indicates that this has not been the case to date, with evidence of both local (e.g., membrane damage) and systemic problems (e.g., obesity) that can be attributed to PD solutions. This issue, termed *"biocompatibility"*—although "bio*in*compatibility" is perhaps more correct, has assumed increasing importance in the last few years. The difficulty facing development of solutions in this area is that it may take many years for problems of biocompatibility to develop, and by the same token, studies of many years duration to demonstrate the benefits of new fluids. This is a problem in a therapy that is used by only 180,000 patients worldwide, which for many is relatively short-term.

This chapter will discuss PD solutions under a number of headings, ranging from electrolyte and acid base homeostasis, through alternative osmotic agents to newer biocompatible fluids. In each case the clinical need for the solution type will be discussed, followed by description and rationale of their formulation, evidence of clinical benefit, and finally a discussion of any problems and limitations associated with their use. The chapter concludes with a discussion of potential future developments, some of which are undergoing clinical trials, others under investigation in animal models.

SOLUTIONS FOR CALCIUM AND MAGNESIUM HOMEOSTASIS

Clinical Need

Patients treated with peritoneal dialysis can be in negative, positive or equal calcium balance. This has led to the development of PD solutions with a variety of calcium concentrations (see Table 28-1), which enable the clinician to control the excretion of these ions, so that in turn it is possible to use additional therapeutic measures, (e.g., phosphate binders and vitamin D analogues) to maintain Ca^{++} and Mg^{++} homeostasis.[2] In general, patients with hypocalcemia in whom hyperphosphatemia is well-controlled a dialysate fluid containing a relatively high concentration of calcium will be required. Lower calcium dialysate will be needed for the patient in whom there is a need to use larger oral doses of calcium containing phosphate binder, and these were originally designed to enable clinicians to use this, as opposed to the more efficient but toxic aluminium containing binders. However, growing concerns over vascular calcification in the dialysis population and its association with increased mortality,[3,4] have led to decreased use of calcium containing binders in an attempt to avoid episodes of hypercalcemia. With the development of newer alternative phosphate binders, for example, resins such as Sevelamer, and lanthanum, hypercalcemia can be minimized further. The impact of calcimimetics in this field is not yet known, although it seems likely that this development will increase only the need for flexibility in controlling calcium losses. The purpose of using a lower magnesium concentration is in the prevention of hypermagnesemia,[2,5] which may itself worsen metabolic bone disease. Reducing magnesium levels, at least in principle, also enables the clinician to prescribe magnesium containing phosphate binders.

Solution Description

It can be seen from Table 28-1 that solutions can be divided broadly into high, above normal ionized calcium concentration, typically >1.5 mmol/L, and low calcium concentration, ranging from 1 mmol/L potentially down to zero, although the latter are increasingly not available. Usually the difference in the cation concentration is compensated for by a change in the chloride content, although some solutions have also been designed to reduce magnesium content because patients with renal failure can develop hypermagnesemia. High calcium solutions are designed to keep the patient close to equal balance for calcium by minimizing dialysate losses. By setting the concentration above the normal ionized Ca^{++} concentration in the blood (for example, dialysate: 1.75 mmol/L verses plasma: 1.2 mmol/L), this is achieved, although the loss of calcium in the dialysate because of convection will modify this. Typically, when using 1.36% exchanges calcium balance will be achieved at a calcium concentration of 1.38 mmol/L, whereas at 2.27% and 3.86% glucose exchanges, this will be at 1.7 and 2.2 mmol/L Ca^{++}, respectively.[6]

Evidence of Clinical Benefit

Patients commencing dialysis treatment are often in negative calcium balance because of accrued metabolic bone disease and poor nutritional status, and the ability of the clinician

TABLE 28-1 Summary of the Composition of the Principle Dialysis Solutions Commercially Available

SOLUTION TYPE AND NAME	ELECTROLYTES (mmol/L)				BUFFER (mmol/L)		
	SODIUM	CALCIUM	MAGNESIUM	CHLORIDE	LACTATE	BICARBONATE	PH
Glucose sol							
Gambrosol trio*	131–133	1.31–1.38	0.24–0.26	95.2–95.4	39–41	—	5.5–6.5
Staysafe 2–4+	134	1.75	0.5	103.5	35	—	5.5
Staysafe 10–12+	134	1	0.5	102	35	—	5.5
Staysafe 17–12+	134	1.25	0.5	102.5	35	—	5.5
Balance 1.25 Calcium+	134	1.25	0.5	102.5	35	—	7
Balance 1.75 Calcium+	134	1.75	0.5	101.5	35	—	7
Bica Vera+	134	1.25	0.5	102	0	34	7.4
Dianeal PD1¶	132	1.75	0.75	102	35	—	5.5
Dianeal PD2¶	132	1.75	0.25	96	40	—	5.5
Dianeal PD4¶	132	1.25	0.25	95	40	—	5.5
Physioneal 35¶	132	1.75	0.25	101	10	25	7.4
Physioneal 40¶	132	1.25	0.25	95	15	25	7.4
Amino acid sol							
Nutrineal¶	132	1.25	0.25	105	40	—	6.7
Icodextrin sol							
Extraneal¶	133	1.75	0.25	96	40	—	5.1

Electrolyte, buffer, and pH formulation is shown for the three worldwide manufacturers of PD solutions (*Gambro, +Fresenius, and ¶Baxter).
To convert from mmol to mEq for calcium and magnesium, multiply by 2.
Where a range is indicated reflects the variability due to different solution combinations derived from a multicompartment bag when reconstituting in order to obtain varying glucose concentrations.

to prescribe a dialysis regime that prevents further calcium loss is important. Testimony to the efficacy of this approach is the relatively high proportion of patients who when treated with calcium 1.75 mmol solution in combination with calcium containing phosphate binders develop hypercalcemia.[7,8] The concentration of Mg^{++} in these solutions is set at the lower end of the normal range for plasma. This is because there is a tendency for this ion to accumulate in dialysis patients. There is evidence that patients using these solutions can develop mild hypermagnesemia, which appears to be of no apparent clinical significance.[5] Magnesium intoxication has not been reported.

The ability of low calcium solutions to achieve negative calcium balance has also been confirmed by cross-sectional studies,[2,9,10] and their clinical efficacy in reducing the incidence of hypercalcemia in patients using calcium containing phosphate binders is well-established in longitudinal studies.[2,8,11] With increasing evidence of the detrimental effect of vascular calcification on survival in PD patients and the poor outcome of individuals with adynamic bone, itself associated with hypoparathyroidism at least in part as the result of relative hypercalcemia, it would seem sensible to favor the use of lower rather than higher dialysate calcium concentrations. Dialysate with lower magnesium concentration has been shown in clinical studies to resolve hypermagnesemia[12] and is associated with normal magnesium levels in plasma.[5]

There are no published clinical trials comparing the efficacy of different dialysate solutions in relation to calcium and magnesium homeostasis in children, although calcium balance studies have been performed.[13] The physiology and clinical problems as outlined previously are essentially the same in children as in adults, with the added concern of adequate growth, and particular emphasis in avoiding aluminium bone disease.[14] Current guidelines favor the use of low calcium concentration fluids[15] to enable concurrent use of calcium containing phosphate binders. Data from the pediatric national registries would indicate that maintenance of growth on peritoneal dialysis in children is reasonable using this strategy.[16,17]

Problems

As might be anticipated, a small proportion of patients treated with lower calcium concentration solutions will experience a rise in parathyroid hormone (PTH) levels,[18] although over 12 months this does not have an adverse effect on bone biopsy.[19] Equally, occasional patients will develop hypomagnesaemia when using a lower concentration of this cation.[20] Clinicians need to be aware of this potential, but entirely predictable problem, by adjusting the oral dose of calcium containing phosphate binders, vitamin D analogues, and calcimimetics, in response to their monitoring of PTH, calcium phosphate product, and markers of bone turnover. The use of very low, or even zero calcium concentration solutions, as a short-term measure in the treatment of severe hypercalcemia is now largely redundant because cinacalcet may be used in preparation for parathyroidectomy and bisphosphonates where malignancy is the cause. In any event their long-term use runs the risk of developing a significant negative calcium balance.

SOLUTIONS FOR ACID-BASE BALANCE

Clinical Need

In replacing the functions of the kidney, there is a requirement to provide buffering capacity to enable excretion of hydrogen ions, continuously produced as a consequence of human metabolism.[21] Peritoneal dialysis fluid must therefore contain a buffer in a greater concentration than it is in plasma to insure net flow across the peritoneal membrane into the patient. There are essentially two issues related to the choice of PD solution that need to be considered in this regard. First, the concentration of buffer required to maintain optimal acid-base status of the patient, and this will be the principal focus of this section. Second, there are issues of biocompatibility that will be dealt with in more detail under the section on biocompatible fluids (6.1–4). Briefly, the buffers that have been used in PD solutions have changed and continue to change as the therapy develops. Initially acetate was used, but this was abandoned following strong circumstantial evidence that it was an etiological factor in the development of encapsulating peritoneal sclerosis. Subsequently, lactate has been widely used, which once it has entered the patient, is metabolized rapidly to bicarbonate.[22] More recently, primarily for reasons of patient comfort and biocompatibility, pH neutral bicarbonate solutions have been developed (see later discussion), although there is potential for superior acid-base control using bicarbonate under special conditions, for example, in children or patients with liver disease.

The efficacy of dialysis treatment in controlling acid base balance, and in particular preventing the development of metabolic acidosis, is usually assessed from measurement of the plasma bicarbonate (or CO_2) concentration.[23] In contrast to hemodialysis patients, who tend to have a fluctuating acid-base status such that they are frequently relatively acidotic before the treatment sessions, patients treated with peritoneal dialysis are usually in a steady state. Typically, 70% of PD patients have a plasma bicarbonate in the normal range, about 12% have low level indicating acidosis, and the remainder mild degrees of alkalosis. In CAPD patients, but not APD patients, there is a modest effect of peritoneal solute transport status on plasma bicarbonate, such that low transport is associated with a tendency for lower levels and vice versa. In both modalities, lower bicarbonate levels appear at least in part to be the result of inadequate dialysis dose. It should also be remembered that buffering capacity is increased by the oral ingestion of drugs such as calcium carbonate, also used as a phosphate binder, and sodium bicarbonate. Although the need to achieve adequate buffering capacity is not in doubt, the optimal target for plasma bicarbonate, as will be seen, is not so clear. The need to achieve stable and adequate control of acid-base status in the pediatric population is if anything more important than the adult population.[24] Poorly controlled acidosis is an important reason for poor growth in children with renal failure. The ability of peritoneal dialysis to provide steady state control of acidosis is one reason why this is a preferred treatment modality in pediatric practice.[25]

Solution Description

The range of buffer types and concentrations that are commercially available are summarized in Table 28-1. Lactate concentrations vary between 35 and 40 mmol per liter. Some

years ago manufactures changed from using the racemic mixture, D(−), L(+) lactate to the L(+) isomer form only. This is of no clinical consequence because the metabolism of both isomers is equally efficient in the human. Bicarbonate containing fluids might be either solely this buffer, ranging from 35–39 mmol/L, at a buffering capacity similar to conventional lactate solutions (buffering capacity is the same mol for mol), or contain a mixture of bicarbonate (e.g., 25 mmol/L) and lactate (15 mmol/L). The rationale for this latter choice is that a bicarbonate solution of 40 mmol/L is supraphysiological and may cause local changes in the microcirculation of the peritoneal membrane. This concern is borne out by the observation that pure bicarbonate solution is associated with significantly more abdominal pain than the mixture.[26] This argument will be developed further when discussing the relative merits of these solutions and their biocompatibility.

Evidence of Clinical Benefit

The combination of bicarbonate obtained from dialysate lactate and the oral phosphate binder, calcium carbonate, has been demonstrated to achieve normal, steady state acid-base status in the vast majority of peritoneal dialysis patients.[23] There is good evidence, however, that not only prevention of acidosis but also maintaining higher plasma bicarbonate, albeit within the normal range, is beneficial in peritoneal dialysis patients. An increase in plasma bicarbonate, if below 26 mol/l, is associated with down regulation of the ubiquitin-proteosome complex in muscle the main mediator of muscle catabolism.[27] In one prospective study of acid-base status, comparison was made between the formulation lactate 35 mmol/L with lactate 40 mmol/L.[28] In this study further attempts were made to make the lactate 35 mmol/L group more acidotic by avoiding calcium carbonate and the lactate 40 mmol/L group more alkalotic by coprescribing sodium bicarbonate. Between-group separation was achieved, such that plasma bicarbonate levels were 23±0.3 and 27.2±0.3 mmol/L at 1 year, that is, both within normal limits. Patients randomized to the high lactate treatment had fewer hospital admissions and gained lean body mass as determined from anthropometrics. In another randomized study, patients who had been acidotic on conventional fluids had better clinical outcomes if their treatment was supplemented with oral sodium bicarbonate.[29] It seems, therefore, that patients on PD are better maintained with a bicarbonate level in the upper part of the normal range.

In adults, a bicarbonate-only solution containing 33 mmol/L when compared to lactate 40 mmol/L did not result in adequate buffering capacity,[30] whereas bicarbonate 34 mmol/L was superior to lactate 35 mmol/L in a nonrandomized study conducted over 12 months.[31] For mixed solutions, there is no clear evidence that substituting bicarbonate for lactate at a high equivalent buffering capacity (40 mmol/L) results in superior acid-base balance in CAPD patients—indeed the mix of bicarbonate to lactate does not seem to matter.[32] However, for solutions with a lower buffering capacity, when patients are switched from an all lactate (35 mmol/L) to a 25 mmol bicarbonate: 10 mmol lactate mix, there is a significant improvement in plasma bicarbonate (24.4 to 26.1 mmol/L), such that a higher proportion of patients had a value within the normal range.[33] Both these solution combinations (bicarbonate 25 mmol/L, lactate 10 or 15 mmol/L) are effective in controlling acid-base in APD patients, although when using the 25/10 combination, there was a significant fall (~1.26 mmol/L) in the plasma bicarbonate after switch from standard lactate (40 mmol/L) solutions. Patients switched from lactate 40 mmol/L to the 25/15 mix were significantly more likely to achieve plasma bicarbonate in the normal range.[34] In an open study of two pure bicarbonate solutions (35 and 39 mmol), benefit was seen when compared to lactate with both concentrations if the baseline plasma bicarbonate was <25.3 mmol/L, but no difference between the two was observed.[35]

A study comparing lactate (35 mmol/L, pH 5.5) with a pure bicarbonate-buffered PD solution (34 mmol/L, pH 7.4) in children suggests that this is safe in the short term,[36] and current recommendations are in favor of using bicarbonate solutions in this patient group.[15] The additional benefits of bicarbonate containing solutions, which by definition are also pH neutral, are of reduced infusion pain,[26,34] and potential benefits to membrane function and host defenses will be discussed under the section on biocompatibility.

In summarizing these findings, it can be said that despite the theoretically equal buffering capacity of bicarbonate and lactate, in patients who are at the acidotic end of the spectrum this can be normalized more efficiently with pure bicarbonate or mixtures with lactate with a total buffering capacity of 35 mmol/L, whereas solutions using lactate alone will require 40 mmol/L.

Potential Problems

There is a tendency for some patients (approximately 17%) to run bicarbonate levels above the normal range, usually when combining high buffering capacity solutions with oral calcium carbonate. Although reported, this has not been demonstrated to result in detriment to the patient with any certainty.[20] This problem is likely to become less of an issue as clinicians move toward using alternative phosphate binders. Failure to achieve adequate control of acidosis will be uncommon with commercially available solutions. By increasing the dialysis dose in anuric patients, using pure bicarbonate >35mmol or 25/lactate 15 mmol/L mix, particularly if on APD and the careful use of added oral sodium bicarbonate, this should always be avoidable. Bicarbonate solutions are not associated with any increase in peritonitis, possibly less,[37] and may be associated with a slight improvement in ultrafiltration in the long term.[38,39]

GLUCOSE AND GLUCOSE POLYMER SOLUTIONS

Clinical Need

Ultrafiltration is an essential component of peritoneal dialysis treatment. Apart from the need to remove water in order to maintain stable fluid status, it is required for the convective component of solute removal. This is proportionally more important for solutes that have a low concentration gradient between blood and dialysate, such as sodium or

calcium,[6,40] and for larger molecules such as β-2 microglobulin that diffuse relatively slowly compared to their mass transport by convection.[41]

There is also increasing evidence that the ability to obtain adequate ultrafiltration has relevance to clinical outcomes that is currently more convincing than for the achievable variability in peritoneal solute clearance.[42] At present, evidence is from observational cohort studies only, and in some cases indirect only, although the weight of evidence is impressive. First, a number of observational studies have found that in CAPD patients that high solute transport is associated with worse outcomes, in terms of both patient and technique survival,[43,44] recently confirmed on metaanalysis.[45] One likely explanation of this association is the negative relationship between peritoneal ultrafiltration capacity and increasing solute transport when glucose is used as the osmotic agent, such that in longer exchanges there is net reabsorption of fluid during a dialysis exchange. Second, several studies have related achieved peritoneal fluid and sodium removal (they are tightly coupled in CAPD patients) to either patient or technique survival.[46,47] The European Automated Peritoneal Dialysis Outcomes Study found that inability to achieve more that a predefined daily ultrafiltration target of 750 ml in anuric patients was associated with worse survival.[48] One of the undoubted factors contributing to this worse ultrafiltration was reduced membrane ultrafiltration capacity to glucose, and NECOSAD reported a very similar relationship between ultrafiltration and survival in anuric patients.[49] More recently a secondary of the ADEMEX study found a net ultrafiltration <400 ml/day to be a predictor of death, independent of comorbidity, inflammation, and residual renal function.[50]

There has also been considerable progress in our understanding of the mechanisms of fluid removal across the peritoneal membrane.[51] There are essentially two pathways of water transport that will work differently with different types of osmotic agent (Figure 28-1). There are water specific pathways, known to correspond to aquaporin channels situated in the endothelium, which are highly efficient but require an osmotic gradient best achieved with small osmolytes such as glucose. There is also a larger set of small pores responsible for allowing the removal of small solutes, for example, creatinine that also enables water removal. These are less efficient when using low molecular solutes, such as glucose, than the aquaporins because they readily permit transport of the osmolyte into the patient, resulting both in a much reduced reflection coefficient but also a drop in the osmotic gradient with time, during the dwell. Once the gradient has dissipated Starlings forces will dictate a reversal of net fluid flow driven by the higher colloid pressures within capillaries. As a result, patients with high solute transport, who have a greater number of small pores, will have less good osmotically driven ultrafiltration with glucose through the aquaporin pathway combined with more rapid fluid reabsorption—predominantly occurring through the small pores—once there is no osmotic gradient.[52] When a larger molecule is used, for example, albumin or a polyglucose (e.g., icodextrin, Extraneal), a sustained ultrafiltration can be achieved during a long dwell because it will remain in the peritoneal cavity for a much longer period.[53,54] In fact under these circumstances, the larger the number of these pores potentially the better, because the achieved ultrafiltration will be proportional to their area. Furthermore, it is possible to achieve net ultrafiltration without creating an osmotic pressure because large molecules, by virtue of their size have colligative properties that will drive convective flow without the need for an osmotic gradient. In the case of albumin, which also has an electrical charge, this is a true "*oncotic*" pressure, a term that is frequently applied to any large molecule, such as a polyglucose, albeit that this is strictly incorrect.

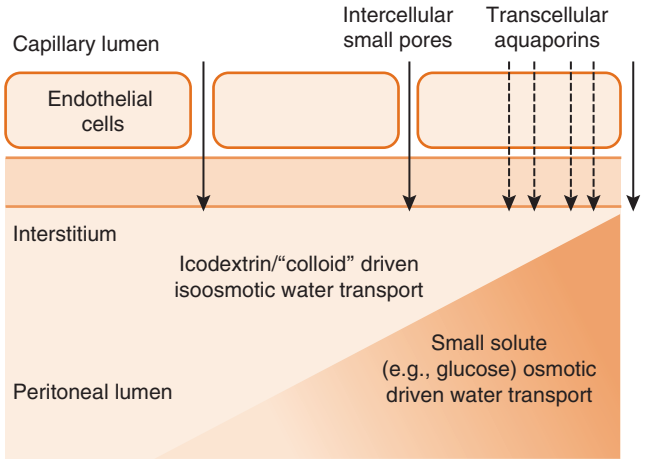


FIGURE 28-1 There are two pathways for ultrafiltration. First, a water exclusive, high-efficiency transcellular pathway due to the presence of aquaporins present in the vascular endothelium that requires an osmotic gradient. Second, an intercellular pathway that is less efficient but still contributes half of the ultrafiltration because it represents the majority of the total pore area. Small osmolytes, such as glucose, amino acids, and glycerol, act across both pathways but require an osmotic gradient. Large molecules, such as icodextrin, are able to exert a "colloidal" gradient across the intercellular pathway.

To summarize, therefore, peritoneal physiology dictates the different types of solution that will be required in order to achieve the best ultrafiltration. There is a need both for small osmotic agents to generate short-term, efficient, ~50% aquaporin mediated ultrafiltration and larger molecules that can achieve long dwell fluid removal, which has properties more similar to albumin, the naturally occurring oncotic agent.

There is another reason why an alternative to glucose is required—the avoidance of the metabolic complications of excessive peritoneal absorption of glucose. Obesity is a well-recognized complication of PD as is associated hyperinsulinemia and lipid abnormalities.[55,56] Longitudinal studies have shown that patients on PD tend to gain fat weight and that this weight gain is associated with a worsening lipid profile.[55,57] With an increasing proportion of dialysis patients being diabetics, who do not always appear to enjoy the same benefit from PD as is seen in nondiabetics,[58] the importance of glycemic control is in need of receiving increased attention.

Solution Description

Glucose: Glucose containing dialysate solutions have been manufactured in three strengths for many years. The concentrations are 1.36%/1.5%, 2.27%/2.5%, and 3.86%/4.25%, (the alternative values represent the anhydrous/hydrated form), and these result in fluids with an osmolality of

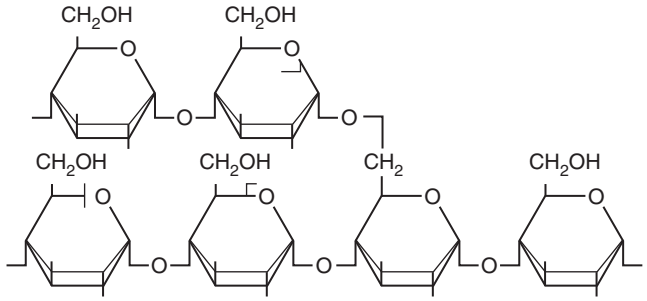


FIGURE 28-2 Icodextrin has a polyglucose structure found in starch; the number of subunit ranges from 2 to 1000; 90% of the linkages between subunits are of the α 1-4 type. The majority fraction, accounting for ~50%, comprises 30–120 subunits with a molecular weight range of 5–20,000 Daltons.

344–347, 395–398, and 483–486 mOsmol/L, respectively. They enable the clinician and patient to vary the dialysis prescription so as to titrate peritoneal fluid removal and thus maintain the desired dry weight.

Glucose Polymer: Icodextrin is the only polyglucose and thus the only large molecular weight solution commercially available. It is currently formulated to be isoosmotic with plasma (284 mOsmol/L) at a concentration of 7.5%, with a sodium concentration of 133 mmol/L and a lactate concentration of 40 mmol/L. As its name implies, it consists of several glucose molecules tagged together, as they are found in starch, from which it is manufactured (Figure 28-2). Although the prefix "*ico*" implies 20 glucose building blocks per molecule, it is in fact a polydispersed mixture of the glucose polymers (range 2–1000 units) found in starch that has been refined to remove the smaller fractions that would otherwise cross the peritoneal membrane more readily and accumulate or be metabolized by the patient. As it is, a significant proportion of the starches do enter the circulation, where they are metabolized eventually to maltose by circulating amylase.[59] In patients using icodextrin for one exchange per day, steady state of these metabolites is reached within two weeks. They do, however, contribute to the osmolality of the plasma, resulting in a variable degree of isoosmotic hyponatremia, usually about 2 to 5 mmol/L lower than the patient's pretreatment plasma sodium.[60] The maltose cannot be metabolized in the circulation of humans, which lacks maltase, although this enzyme is present in the kidney and intracellularly throughout the body. There is no evidence to date that maltose accumulates within patients treated with icodextrin.

Evidence of Clinical Benefit

Glucose Solutions: Glucose is a highly effective osmotic agent that was well-established in the use of Intermittent Peritoneal Dialysis before the inception of CAPD and APD. Its undisputed efficacy combined with its low cost means that it is always likely to have a role in this treatment modality. Carefully conducted single dwell studies have confirmed that the initial ultrafiltration rate across the peritoneum is directly proportional to the initial glucose osmotic gradient.[61] Glucose solutions have also become the standard for assessing peritoneal membrane function. Generally, using a standardized 4-hour dwell period, patients achieving more than zero net ultrafiltration (or >200ml if including the systematic overfill of the dialysis bag for flush purposes) when using a glucose 2.27%/2.5% (standard Peritoneal Equilibration Test)[62,63] or more than 400 ml with a glucose 3.86%/4.25% exchange (simplified Standardized Permeability Analysis)[64] will be able to obtain sufficient overall daily ultrafiltration (Davies, 2001 #2574). Values below this indicate relative ultrafiltration failure, although this might not manifest clinically until the residual urine volume of the patient has become critically low.

Glucose dialysate also has the potential of being an important calorie source for patients who are malnourished. Adequate calorie intake appears to be important in maintaining nitrogen balance, especially in long-term PD patients,[65] and it should be remembered that when the dialysis dose is increased, there is inevitably an increase in delivered calories form this route, which may be of help in maintaining nutrition in the malnourished.[66]

Glucose Polymer: There is now considerable clinical experience with icodextrin, a PD solution that has been subjected to more randomized clinical trials than any other (Table 28-2). Used as salvage therapy in patients with clinically inadequate ultrafiltration, it can extend the life of PD treatment.[67] When used on a daily basis for the long exchange (overnight in CAPD and during the daytime in APD patients), it results in net ultrafiltration that is equivalent to that achieved using 2.27%-3.86% glucose, depending on length of dwell and peritoneal membrane function.[68] Generally, the longer the dwell means that more ultrafiltration will be obtained, although there is rarely any value in extending beyond 14 hours. On average, it is slightly more effective in patients with high solute transport, in keeping with its proposed mechanism of action across the small pores, although there is considerable individual variability. As a rule of thumb, icodextrin will achieve significantly better ultrafiltration than glucose 2.27% in patients with high or high average solute transport characteristics (D/P creatinine ration at 4 hours >0.64),[69] and this is why this has been the main comparator solution used in the randomized studies. In high average and high transporters, the ultrafiltration volume with use of icodextrin for the long day dwell is significantly superior than obtained with 3.86% glucose.[179] As a result of better convection, icodextrin will also remove more sodium when compared to glucose 2.27%.[70] The diffusive removal of sodium, however, is not so well-optimized. The length of the dwell ensures that there is time for equilibration, but the sodium gradient is compromised, partly because the concentration of sodium in the dialysate is 133 mmol/L (compared to 132 mmol/L in conventional glucose solutions) but also because patients on icodextrin develop a relative hyponatremia, which influences sodium removal throughout the rest of the day. Nevertheless, provided better ultrafiltration is obtained, icodextrin will achieve better overall sodium losses.

There is evidence that this improved fluid removal translates into changes in weight, fluid status, and body composition. In a large randomized trial comparing icodextrin to glucose 2.27% over 12 months, a divergence in weight was observed, such that weight gain was prevented in the patients treated with icodextrin.[69] This could be the result of either fat or fluid gain in the glucose-treated patients or the opposite, including loss of lean body mass in the

TABLE 28-2 Summary of Randomized Controlled Trials Establishing the Safety and Efficacy of Icodextrin

AUTHOR, YEAR, REFERENCE	N	LENGTH	COMPARATOR FLUID (DESIGN)	COMMENTS
Mistry, 1994[68]	I: 106 G: 103	6 months	1.36% or 3.86%	MIDAS study: ultrafiltration compared to 1.36% was 3.5 times greater for 8 hours and 5.5 times greater for 12-hour dwell length and equivalent to that achieved with 3.86% exchanges.
Gokal, 1995[175]				Using icodextrin for the long dwell in CAPD neither increases the rate of peritonitis nor alters the outcome of peritonitis. Peritonitis does not affect uptake of icodextrin from the peritoneum.
Posthuma, 1997[176]	I: 11 G: 12	12 months	2.27%	Icodextrin enhances ultrafiltration during the daytime dwell in CCPD patients, increasing convective clearance of creatinine.
Postuma, 1997 & 1998[60,177]	I: 19 G: 19	12 months	2.27%	Icodextrin preserved the daytime dwell ultrafiltration in CCPD patients during peritonitis. Serum icodextrin metabolites increased during icodextrin use, accounted for the osmolar gap, and associated hyponatremia, but remained stable during peritonitis.
Plum, 2002[70]	I: 20 G: 19	12 weeks	2.27%	Icodextrin produced increased, sustained ultrafiltration during the long dwell period, increasing (convective) clearance and sodium removal in APD patients. No effect on residual function.
Wolfson, 2002[69]	I: 90 G: 85	4 weeks	2.27%	Efficacy study showing that icodextrin increases UF in long dwell, preventing fluid reabsorption. Greatest comparative benefit to glucose observed with higher solute transport.
Wolfson, 2002[69]	I: 175 G: 112	52 weeks	2.27%	Safety study showing a significant difference in body weight between groups (lower with icodextrin, gain with glucose) when compared to baseline.
Guo, 2002[82]	I: 58 G: 35	13 weeks	2.27%	Peritoneal dialysis patients treated with icodextrin experienced substantial quality of life improvement at 13 weeks after the start of treatment, in particular, improvement of patients' mental health, general health, and symptoms such as muscle spasms or twitching, cramps during an exchange or treatment, cramps after an exchange or treatment, itchy skin, and faintness or dizziness.
Konings, 2003[71,93]	I: 22 G: 18	4 months	1.36% (Open label RCT)	Patients randomized to icodextrin experienced a large increase in UF, reduction in extracellular fluid volume, left ventricular mass and weight, and a small but significant reduction in urine volume. No changes in glucose group. No changes in BP or CRP.
Davies, 2003[72,94]	I: 28 G: 22	6 months	2.27% (Double blind RCT)	Icodextrin patients achieved greater ultrafiltration, sodium removal, weight loss, and a reduction in extracellular fluid volume. Weight in glucose patients increased without increase in body water, suggesting fat gain. Residual renal function better preserved in the icodextrin group. No change in BP, CRP, or lipid profiles.
Ota, 2003[178]	18	3 months	1.36% (Open, crossover)	Confirms better UF in Japanese PD patients with icodextrin. Peritoneal absorption of fluid ranges between 36% and 42%.
Finkelstein, 2005[179]	I: 47 G: 45	2 weeks	4.25% (Double blind RCT)	Icodextrin achieves better ultrafiltration than hypertonic glucose in the long exchange and prevents any fluid reabsorption in high/high average transport patients. Rash more frequent with icodextrin.
Paniagua 2008, 2009[73,79]	I: 30 G: 29	12 months	2.5% (Open label RCT)	Multicenter study of diabetic patients. Icodextrin was associated with better metabolic control (assessed by glycosylated hemoglobin), triglycerides, fluid status, blood pressure, echocardiography, and fewer diabetic complications.

G, glucose; *I*, icodextrin. See Table 28-3 for randomized trials combining icodextrin and amino acids.

icodextrin treated group. More detailed studies in smaller patient groups, using more sophisticated techniques such as bioelectrical impedance, isotope dilution methods and DEXA scan, have shown that weight loss in patients randomized to icodextrin results from loss of fluid from the extracellular compartment.[71,72] In the latter study, conducted over 6 months, there was also a weight gain in the patients randomized to glucose, supporting the findings of the 12-month study cited previously. This weight gain was not fully explained by increases in fluid status, implying that there was also an additional increase in body fat.[72] These improvements in fluid status are also seen in diabetics and are associated with improvements in blood pressure and left ventricular end-diastolic diameter.[73] The benefits for blood pressure control are less clear in nondiabetics; with the exception of one single-center, open study,[74] randomized studies have not shown a significant effect on blood pressure.[71,72] Blood pressure control in these studies has been good in both randomized groups, however, which were designed to give maximum freedom to the clinician in terms of antihypertensive drug prescription.

Prevention of obesity and efficacy in diabetic subjects emphasizes the metabolic advantages in using icodextrin when compared to the more hypertonic glucose solutions. In nondiabetic subjects, the hyperinsulinemia associated with the continuous use of glucose containing solutions is significantly improved by the use of icodextrin, and this is associated with an improvement in insulin sensitivity.[75,76] The effect of icodextrin on lipid profiles has been variable, although there is evidence that they can improve when using icodextrin.[76,77] The reason for these discrepancies may well reflect the fact that many PD patients are already receiving

lipid-lowering treatment when they commence icodextrin.[72] In diabetic subjects, both short- and long-term glycemic control has been shown to improve in randomized studies[78,79] and this was associated with improved lipid profiles in an observational Japanese study.[80] Gastric emptying, which is delayed in PD patients and may be responsible for lack of appetite, is less marked when using icodextrin than glucose.[81]

Apart from extending life of therapy, avoiding some of the detrimental metabolic effects of glucose and improving both achieved ultrafiltration and fluid status, there is evidence that use of icodextrin improves the quality of life of PD patients. In the short-term (13 weeks) patients randomized to icodextrin reported better physical and mental health status than those using standard glucose.[82]

Potential Problems

Glucose Solutions: The problems associated with using glucose solutions are threefold. First, there is the issue of local tissue damage to the peritoneum, which will be discussed later under bioincompatibility. Second, there are the unwanted systemic metabolic effects, which have largely been dealt with. Third, there is a more general problem associated with the use of any osmotic agent that relies substantially upon its effects across the aquaporins to achieve ultrafiltration. Precisely because this mechanism of ultrafiltration is water exclusive, solutes such as sodium that are dependent on convection for their loss may not in fact be removed so efficiently because of their sieving by these pores. When APD is used with multiple short exchanges hypertonic glucose, there might be quite efficient ultrafiltration but insufficient time for the diffusive component of sodium loss to occur. This leads to relatively poor sodium losses in APD patients, despite apparently good ultrafiltration, an issue of which the prescribing clinician should be aware.[83] There is some evidence to suggest that APD patients have less good blood pressure control, perhaps for this reason,[84] and certainly anuric APD patients with poor ultrafiltration (<750 ml/day) seem by whatever mechanism to have worse clinical outcomes.[48] Optimizing daytime ultrafiltration, for example, with icodextrin, can ameliorate the problem.[83] Nevertheless, analysis of data from the Australia and New Zealand registry and from the United States Renal Data System suggests that there are no significant differences in risk for either death or transfer to hemodialysis in patients treated with continuous ambulatory and automated peritoneal dialysis.[198,199]

Glucose Polymers: As discussed, there is absorption of glucose polymer fractions across the peritoneum, which results in a number of potential problems of which the clinician needs to be aware. First, these polymers and their metabolites reach a steady state in plasma between one and two weeks on treatment. The slight hyperosmolality that they cause, combined with its associated hyponatremia, does not appear to have any clinical adverse effects. It does result in some reduction in the efficacy of icodextrin as an ultrafiltration agent, however, and patients who initially report very high ultrafiltration volumes may see a modest reduction with time. The presence of icodextrin and its metabolites in plasma can also interfere with some analytical methods. For example, certain blood sugar measuring devices that use glucose dehydrogenase-pyrroloquinolinequinone will overestimate the blood sugar,[85,86] whereas the usual method for determining plasma amylase in the diagnosis of pancreatitis is unreliable because of its underestimation.[87]

The other potential problem with the use of icodextrin is the development of allergies and sterile peritonitis. Skin rashes are well-described and appear to be the result of an allergic reaction to starch.[88] Usually these are mild, localized, and typically occur on the palm of the hand. In most cases they are transient and the patients can put up with them until they resolve over a few weeks. Occasionally (1%-3% of patients), the patient develops an exfoliating dermatitis that is often generalized and can be quite severe, causing erythroderma.[89] In these situations the icodextrin should be withdrawn and not reintroduced and the problem will recur. Sterile peritonitis in patients using icodextrin and miniepidemics of this problem have been described.[90] At least one of these outbreaks was found to be the result of contamination of the icodextrin solution by peptidoglycan, the product of bacterial cell walls that were contaminating the refining of raw product. Typically patients with this problem have a sterile peritonitis that does not respond to antibiotics, which on differential white cell count is associated either with raised eosinophils or mononuclear cells but not neutrophils.[91] The patient is not usually unwell, and the problem responds very rapidly to withdrawal of the product. Although this problem has been identified and largely put right by tightening the quality controls of fluid production, isolated cases of icodextrin-associated sterile peritonitis are occasionally reported. Importantly, however, none of the controlled trials (see Table 28-2) have reported a higher incidence of peritonitis using icodextrin.

Concern has been expressed that too rapid ultrafiltration induced by icodextrin might precipitate a significant fall in residual renal function. There is certainly increasing evidence that episodes of volume depletion, intentional or otherwise, are associated with a fall in urine volume.[92] The majority of randomized trials using icodextrin have not shown any significant differences in the effect of icodextrin compared to glucose. In the detailed study in which icodextrin was compared to glucose 1.36% solution, a very large increase in average ultrafiltration (from 744 to 1670 ml/day) was associated with a fall in urine volume (1131 to 913 ml/day) because of significant dehydration in four subjects.[71,93] In contrast, the change and between-group difference in ultrafiltration, typically 400 ml/day, was more modest in patients selected for greater risk of fluid-related problems (urine volume <750 ml, high or high average solute transport), using glucose 2.27% as the comparator fluid.[72] Secondary analysis of this study found that in both groups, there was a relationship between changing fluid status and residual renal function, but the latter was better preserved in patients randomized to icodextrin despite a similar average reduction in extracellular fluid volume.[94] The conclusion that should be drawn is that sudden large increases in ultrafiltration should be avoided in PD patients (by whatever fluid regime), and that provided icodextrin is introduced carefully, it is possible to achieve the desired effect safely.

AMINO-ACID SOLUTIONS

Clinical Need

It is well-recognized that many patients on dialysis treatment are, or become, malnourished. It is also known, especially for peritoneal dialysis patients, that malnutrition is an

independent predictor of poor survival.[48,95] The causes of malnutrition are, however, complicated. Reduction in renal function is associated with a spontaneous fall in appetite,[96] which does to some extent improve following the commencement of dialysis treatment,[97] although this is certainly reduced once residual renal function is lost.[98] There is also evidence that positive nitrogen balance is better maintained in the short-term when protein intake is high, although in longer-term PD patients-it may be that adequate calories derived from carbohydrate are important.[99] It is increasingly clear, however, that protein-calorie malnutrition is also influenced by comorbid disease, in particular cardiovascular atheromatous disease when associated with an inflammatory state.[100] PD patients with increasing comorbidity, now known to be the dominant determinate of survival on dialysis, report reduced dietary protein and calorie intake for a given small solute clearance (Davies, 1995 #67) and generally fail to improve their intake following an increase in delivered dialysis dose.[66] In patients who cannot, or will not eat, it is tempting to try an alternative approach to delivering nutrition—hence the development of amino-acid containing solutions.

There is, however, another perhaps equally important clinical need for an amino-acid solution—an alternative low molecular weight osmolyte to glucose, for reasons both discussed previously and later in further detail, when considering biocompatibility.

Solution Description

The only commercially available dialysate fluid containing amino acid is a 1.1% solution (see Table 28-1 for description) that exerts sufficient osmotic force to give an average ultrafiltration equivalent, or a little more, to that achieved with glucose 1.36%. It contains 87 mmol/L of amino acids, the majority (61%) being essential amino acids.

This is not the only amino acid solution that has been formulated over the last 20 years and several different formulations have been evaluated. The aims of solution design have been to give the patient sufficient nitrogen in the form of amino acids to at least replace the nitrogen losses associated with both peritoneal amino acid (3–4 g/day) and protein losses (4–15 g/day), and if possible to normalize the plasma amino acid profile that is associated with uremia and acidosis. In the early stages of solution development a number different amino acid concentrations were investigated, ranging from 1%-2.7% in concentration, in order to establish their osmotic effectiveness, effects on membrane function, absorption profiles, and their potential for inducing acidosis.[101–103] Typically 72%-82% of amino acids are absorbed, with a peak in amino acid concentrations in the plasma occurring by 1 hour. The higher concentration solutions (e.g., 2.7%) resulted in increased estimates of solute mass transfer indicating a vasodilatory effect on the peritoneal membrane,[104] possibly mediated by locally generated prostanoids or nitric oxide.[105] They also resulted in nonphysiologically high concentrations of amino acids and were thus abandoned. Even the 1.1% solution has a small but detectable effect on peritoneal blood flow, resulting in a small but significant increase in small solute transport.[104] Earlier amino acid formulations resulted in excessive acidosis because of the catabolism of lycine, arginine, and methionine, which when replaced by anionic amino acids was largely prevented.[106]

Evidence of Clinical Benefit

Initial balance studies were able to establish that the nitrogen absorbed in the form of amino acids from a single daily dwell of 1.1% solution is sufficient to counterbalance the losses associated with amino acid and protein, in the daily dialysis effluent. The typical amount of amino acids adsorbed per day is 18 g, which, if compared to oral protein, would represent about one quarter, typically 0.3 g/kg, of the daily recommended intake.[101,107] One advantage of this method of delivery is that it avoids the phosphate load associated with the equivalent dietary protein and thus the need for phosphate binders. Furthermore, improvement but not normalization of the plasma amino acid profile has been reported.[108] Thus the primary aims of solution design are largely successful. However, in order to provide convincing evidence of clinical benefit, three further things are required. First, demonstration that nitrogen from amino acid absorbed from the peritoneal cavity can be incorporated into somatic protein. Second, that patients with impaired nutritional can show an improvement, and third, if possible, that this translates into improved clinical outcomes (see Table 28-3).

Detailed studies using ^{15}N-glycine, $^{2}H_3$ leucine, and ^{13}C leucine have shown that of the total amino acid dose, 55% is absorbed by 1 hour and 80% by 5 hours; about half (48%) is used for protein synthesis, whereas a significant proportion (16%) is oxidized as an energy source during the dwell period.[109,110] By giving the patient an oral calorie meal at the same time as the amino acid solution is used, the proteolysis that occurs during this period can be reduced by 25%.[110] Amino acids delivered through the peritoneal cavity can, therefore, be incorporated into protein, specifically skeletal muscle[111] and where possible patients should be encouraged to consume a calorie rich meal or snack, typically 600 kcal, during the course of the exchange, or alternatively should be combined with glucose containing fluids, for example in an overnight APD regime.[112]

Several randomized controlled trials have been performed to evaluate the safety and efficacy of amino acid solutions in PD patients with varying degrees of nutritional status. Summarized in Table 28-3, along with open studies describing clinical experience, these have given mixed, although generally encouraging results. Smaller, earlier studies evaluating precursors to the current commercially available solution failed to demonstrate clear benefit and noted variable beneficial or no effects on plasma lipid profiles. A later multicenter study of malnourished patients studied for just three months demonstrated an increase in circulating IGF in patients randomized to amino acid solution, suggesting an increase in protein synthesis.[113] In a subgroup of patients with a plasma albumin below 35 g/L at the start of the study, those randomized to amino acids had increases in the plasma prealbumin and transferrin levels but no increase in midarm muscle circumference (MAMC). In contrast, those with albumin levels above 35 g/L at baseline showed fewer changes in plasma proteins (if anything these deteriorated in the glucose group) but did experience an increase in MAMC if using amino acids. The only long-term (3 years) randomized study of

TABLE 28-3 Summary of Clinical Trials Examining Safety and Efficacy of Amino Acid Solutions

AUTHOR, YEAR, REFERENCE	N	LENGTH	TRIAL DESIGN	COMMENTS
Bruno, 1989[103]	6	6 months	Open label, cross over	1% AA solution. Nitrogen balance became positive and patients gained weight. Lipid profiles improved significantly and AA profiles became more normal.
Young, 1989 [180,181] Dibble, 1990[182]	8	12 weeks	Open, nonrandomized	Malnourished patients (albumin <35 g/L). 1% solution. Lipids improved (LDL cholesterol fell). Modest benefit in nutrition only. No changes were seen in body weight, body fat, arm muscle circumference, fasting plasma glucose, insulin, growth hormone, triglyceride, nonesterified fatty acids, or HDL cholesterol.
Faller, 1995[183]	15	3 months	Open, nonrandomized	Evaluation of a 1.1% solution. Albumin and transferrin improved significantly. Plasma urea but not bicarbonate increased.
Kopple, 1995[109]	19	20 days	Open, nonrandomized	Detailed in-patient nitrogen balance studies in malnourished patients. 1.1% solution made nitrogen balance significantly more positive.
Jones, 1997[106]	12	14 days	Randomized cross over	Study to evaluate a modified 1.1% AA formula containing reduced lysine, arginine, and methionine to reduce acidosis. Despite a good total protein/nitrogen intake, bicarbonate was higher with modified solution.
Mirsa, 1997[184]	18	6 months	Randomized cross over	The use of 1.1% AA, although clinically safe and without side effects, had no effect on the dyslipidemia in these CAPD patients.
Jones, 1998[107]	20	2–3 days	Open label, cross over	Using a 1.1% solution daily losses of AAs and proteins into dialysate are more than offset by gains absorbed from one exchange; such net gains exceeded losses in all patients studied.
Jones, 1998[113]	AA:54 G: 51	3 months	Randomized open label	1–2 exchanges daily of 1.1% AA solution is safe and provides nutritional benefit for malnourished PD patients (anthropometrics and insulin like growth factor) while improving plasma phosphate levels.
Grzegorzewska, 1999[115]	8	6 months	Open, nonrandomized	Overnight administration of 1.1% solution using concomitant antacids to avoid acidosis. Relatively well-nourished CAPD patients, resulted in increased serum concentration of AAs without changes in other nutritional parameters.
Plum, 1999[185]	10	6 hour dwell	Randomized cross over	1%, bicarbonate buffered solution compared to both bicarbonate and lactate buffered glucose (1.5%). Reduced serum glucose concentrations were found with AA solution, but bicarbonate buffering (34 mmol/L) did not change blood acid-base status combined to either glucose or AAs.
Qamar, 1999[116]	7	3 months	Randomized cross over	Only randomized study in children. Caloric intake increased and protein intake improved. Appetite and total body nitrogen increased in at least half of the children during AA dialysis. Total plasma protein and albumin concentrations did not change significantly.
Van, 2002[81]	61	Single dwell	Randomized cross over	PD patients have impaired gastric emptying even when empty of dialysate fluid. This is worse with glucose instilled that included either AA or icodextrin.
Marshall, 2003[78]	8	72 hours	Randomized cross over	Glycemic control (both concentration and variability determined from continuous measurements) was improved in insulin-dependent diabetics with a dialysis regimen that included AA and icodextrin.
Li, 2003[114]	60	3 years	Randomized open label	Long-term administration of amino acid dialysate is well-tolerated, tends to improve nutritional status in high-risk patients, especially women, but does not alter patient survival.
Tjiong 2007[112]	12	Single dwell	Randomized cross over	Dialysate that contains AA plus G also improves protein synthesis in fed CAPD patients. The use of such a mixture may contribute to long-term improvement of the nutritional status in malnourished CAPD patients with deficient food intake.

AA, amino acid solution; *G*, glucose solution.

amino acid solutions was performed in malnourished Chinese PD patients and examined clinical outcomes, although was probably not sufficiently powered to detect a difference in patient survival.[114] Of the 60 patients randomized, both groups had similar mortality, hospitalization duration, serial C-reactive protein levels, and drop-out rates during the study. Patients using amino acids had an improvement in triglyceride levels, and more stable biochemical markers of nutrition (e.g., albumin, total cholesterol), combined with an increase in the appearance of nitrogen and a reported increase in dietary protein intake. Anthropometrics improved, especially in women in the amino acid treated group, but composite nutritional scores were no different.

In summary, the true benefits of amino acid solutions used in malnourished patients remain equivocal. Certainly they are absorbed and used in healthy PD patients, but it is likely that their relatively disappointing effect in malnourished patients reflects the underlying difficulty of reversing this problem in dialysis patients in whom comorbidity, combined with associated inflammation, is blunting the therapeutic effect. The potential benefit to lipid profiles is also variably reported. It is perhaps more logical to use amino acid solution as part of a dialysis regimen that prevents the use and complications associated with heavy use of glucose solutions, for example, in improving glycemic control in diabetics,[78] improving gastric emptying,[81] and preventing fat gain and associated hypertriglyceridemia and even membrane

preservation (see later) with a hope that protein-calorie malnutrition maybe prevented to some extent.

Potential Problems

The most common side effect seen in patients using amino acid solutions is increased nausea and anorexia. The former may be reported in association with the very slight odor that some patients detect or reflect the modest increase on plasma urea levels that might be observed. In these circumstances there may be symptomatic benefit from increasing the dialysis dose. Some patients will develop mild evidence of metabolic acidosis, manifested by a fall in the plasma bicarbonate.[103,109,115,116] This can almost always be corrected by adjusting the dialysate buffer in the remaining exchanges, adding sodium bicarbonate or calcium carbonate to the medications or again increasing dialysis dose, as a negative relationship between plasma bicarbonate levels and urea clearance has been reported.[23] It is strongly advised that the product is used in combination with expert dietetic support to ensure that the solution supplements rather than replaces adequate total calorie intake.

BIOCOMPATIBLE SOLUTIONS

Clinical Need

The degree of biocompatibility of a treatment might be considered as its lack of interference with normal physiological function while at the same time achieving the desired therapeutic effect. It has been formally defined as "the ability of a material, device, or system to perform without a clinically significant host response in a specific application."[117] As already discussed, the instillation of high glucose concentrations within the peritoneal cavity undoubtedly affects systemic physiology in a fashion that can be considered bio*in*compatible. The purpose of this section, however, is to discuss biocompatibility of PD solutions locally within the peritoneal cavity, and specifically their interaction with the peritoneal membrane, specifically its biology and function. The need to develop biocompatible solutions derives from several strands of evidence that, although largely circumstantial, taken together make a very powerful case. These lines of evidence include the intrinsically bio*in*compatible nature of standard fluids, including their established in vitro and ex vivo toxicity, and the demonstration of both functional and morphological changes to the peritoneal membrane that culminate in ultrafiltration failure and, in the worst cases, sclerosing encapsulating peritonitis.

Bioincompatibility of Standard Fluids: This can be conveniently divided into short-term toxicity, associated with low pH, high osmolality, and the use of lactate as buffer, and long-term toxicity because of the damaging effects of glucose, either because of direct cellular toxicity, the formation of glucose degradation products as a consequence of the sterilization procedure or the formation of advanced glycosylation end-products within the membrane or systemic circulation.

The *short-term* effects of bioincompatibility result in infusion pain, experienced by many patients but considerably variable in severity, combined with cellular toxicity shown in both in vitro and ex vivo studies.[26] Because of the insistence by regulatory authorities throughout the world to heat sterilized PD solutions, this has to be performed at low pH to prevent gross caramelization of glucose. As a result, for the first 45 minutes or so of a dialysis exchange, the intra abdominal fluid is at an unphysiologically low pH that causes a fall in the intracellular pH of local cell populations (macrophages, mesothelial cells), which is potentiated in its toxicity by the presence of lactate.[118] This results in repeated damage to the local host-defense mechanism and the mesothelial cell lining of the luminal surface of the membrane that is thought to have a protective and modulatory role in membrane damage and prevention of inflammation.[119,120] This damage is always exacerbated when solutions of higher osmolality are used.

Standard dialysis fluids also contain glucose degradation products (GDPs), which along with glucose are thought to contribute more to the *long-term* bioincompatibility of these solutions.[121] Generally these molecules, which are highly reactive and toxic to cells, are formed from the nonenzymic autocatabolism of glucose within the dialysate during sterilization that is accelerated by heat and slowed down at low pH. The exception might be acetaldehyde, which also results from catabolism of lactate. Extended shelf life will also increase their concentration in dialysate, especially if the storage has been at room temperature or even higher *(Anders Wieslander, personal communication, data awaiting publication).* The list of culprits is growing steadily (Table 28-4), and some, in particular, are thought to be especially toxic (e.g., 5-hydroxymethyl-2-furaldehyde). However, long-term toxicity might also result from glucose exposure by at least two other mechanisms: the intracellular toxicity of high glucose concentrations resulting in hypoxia because of excess metabolism through the sorbitol pathway and the formation of advanced glycosylation end-products, (AGEs) resulting in damage to extra and intracellular proteins.[122] This latter mechanism is again nonenzymic and is thought to occur in situ within the peritoneal membrane where glucose concentration may be very high, simulating an extreme diabetic milieu.

TABLE 28-4 Glucose Degradation Products (GDPs) Found in Commercial Dialysate Fluids and Markers Used to Identify Systemic GDP and Advanced Glycosylation End Products (AGEs)

Glucose Degradation Products
Acetaldehyde[186–190*]
Formaldehyde[139,188*]
Glyoxal[139,156,188,191,192*]
Methylglyoxal[139,156,188,190–192*]
3-deoxyglucasone[193]
3,4-dideoxy-glucasone-3-ene[193]
5-hydroxy-methyl-2-furaldehyde[139,189,194,195*]
2-furaldehyde[188,195]
Systemic Markers of GDPs and AGE Formation
Plasma fluorescence[190]
Nepsilon-carboxymethyllysine[156]
Imidazolone[196]
Pyrraline[190,197]
Pentosidine[156]

*Significantly reduced in biocompatible dual or triple bag systems.

Functional and Morphological Changes to the Membrane: There is now convincing evidence from longitudinal studies that peritoneal membrane function changes with time on treatment. There is considerable variability between patients, but the overall pattern is one of increasing rates of small solute transport and reductions in the ultrafiltration capacity of the peritoneal membrane.[98,123] The latter is mostly explained by the increases in solute transport, which accelerates the rate of glucose absorption across the peritoneal membrane, thus causing earlier loss of the osmotic gradient during any dwell. This rise in the solute transport rate is thought to reflect an increase in the effective peritoneal surface area, such as would occur with increasing vascularity of the membrane. There is now, however, increasing evidence that a second process is contributing to loss in ultrafiltration capacity with time on treatment.[124] This latter process results in a reduction in the osmotic conductance of the membrane—literally less ultrafiltration for a given osmotic gradient—that is likely to result from reduced fluid permeability of the membrane that can be explained, at least theoretically, by the development of fibrosis.[125,126]

These functional alterations in the membrane are associated with important morphological changes with time on treatment. Although it is difficult to perform longitudinal studies of membrane morphology, data from the Peritoneal Biopsy Registry have built a convincing picture of what appears to happen.[127–129] The two overwhelming abnormalities observed with increasing severity when associated with time on treatment have been a thickening of the submesothelial compact zone and the development of a diabetiform occlusive vasculopathy of the small arterioles and post-capillary venules (Figure 28-3). There was a modest increase in vessel numbers, although it should be remembered that the capillary circulation is responsible for the bulk of solute diffusion, and further examination of this aspect of morphology is still awaited. Other studies have reported increased capillary vessels and this has also been reported consistently in animal models of PD solution exposure.[130]

How can these morphological changes be linked to functional changes of the membrane? There are only two studies so far linking morphology and function, but both show that worse membrane damage is associated with worse function, in one case a link between high solute transport and fibrosis,[131] the other with increased area of microvessels.[130] These observations support the concept that increasing small solute transport results from a greater vascular surface area, whereas reduced osmotic conductance is associated with progressive membrane fibrosis. In some patients a much more severe, encapsulating peritoneal sclerosis forms, often after stopping PD, which causes functional bowel obstruction that frequently requires major surgery.[132] It is likely that dialysis fluid incompatibility is a major contributor to this condition, even though it occurs in only a minority of patients because the main risk factor is time on therapy.

Solution Description

The ideal biocompatible solution would have a physiological pH, use bicarbonate as its buffer, contain no GDPs, be isoosmotic, and only contain osmotic, agents in concentrations that are not toxic to human tissue. No such single solution can exist, however, as without the presence of an osmotic gradient, short-term ultrafiltration, which will always be needed, cannot be achieved. Nevertheless, solutions are

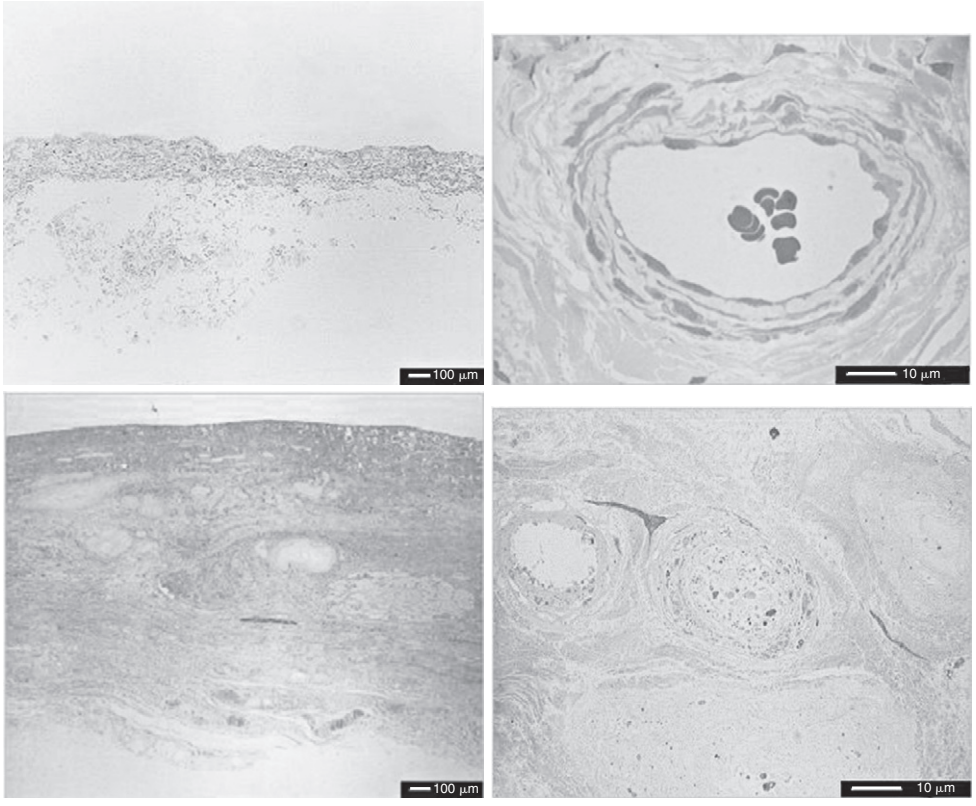


FIGURE 28-3 Images from the Peritoneal Biopsy Registry showing the two most striking abnormalities found in long-term peritoneal dialysis, thickening of the submesothelial compact zone *(left lower panel compared to upper),* and an obliterative diabetiform vasculopathy *(right lower compared with upper panel).* (Photographs courtesy of Professor John Williams, Cardiff, UK.)

now available that go some considerable way towards meeting these objectives. As already discussed, glucose can be avoided by using either amino-acid solutions or polyglucose (icodextrin), and the latter is also isoosmotic with plasma and contains less GDP than conventional glucose 1.36% solutions.[133]

The development of pH neutral solutions has necessitated a different approach, however, with the use of dual or triple compartment dialysate bag technology. In each case the principle underlying this approach in the same, although different manufacturers have come up with differing designs. By using more than one compartment during the manufacturing process, it is possible to do two things. First, by confining the glucose to a compartment with a very low pH, (optimally ~3.5), then during the sterilization process, the formation of GDPs is minimized. Second, when the two components of the dialysis fluid are brought together, just before instillation by the patient—performed by manually breaking a small septum—the final solution can be made to have a normal pH. Second, this general model can be also be used to enable the predominant buffer to be bicarbonate by separating this from magnesium during storage, preventing its precipitation. In addition, by using a third compartment, the potential number of recombinations can be increased, enabling all three glucose concentrations to be obtained from the same bag, for example, Gambrosol Trio.

Evidence of Clinical Benefit

A considerable number of studies have demonstrated that normal pH and low GDP solutions result in reduced cellular toxicity in vitro and improved function of cell populations derived from dialysate effluent when examined ex vivo.[134–138] Mesothelial cell layers when grown in culture as a monolayer, similar to that seen on the surface of the peritoneal membrane, may be physically damaged by scratching with a needle. Their subsequent ability to regrow to confluence is inhibited by standard high GDP solution but unaffected by low GDP fluids.[139] There is, however, a problem when it comes to demonstrating the benefit of these solutions in the prevention of long-term functional and morphological changes to the peritoneum. Studies that involve serial biopsies of the membrane are difficult to justify on ethical and practical grounds, and both functional and morphological changes take many years to develop, which, when combined with high drop-out rates, mean that they are not financially viable. Furthermore, the equipoise of many clinicians is such that the justification for the use of biocompatible fluids can be made on a priori grounds, and if cost implications were not an issue, that it would be unacceptable to randomize patients to bioincompatible solutions.

Nevertheless, this difficulty has led to another approach, namely the use of biomarkers within peritoneal dialysis effluent that act as surrogate measures of peritoneal damage or integrity. The example most studied is the cancer antigen, CA 125, which is a product of mesothelial cells usually used to track the bulk of tumors derived from this cell type. It has been demonstrated that CA 125 is present in dialysate effluent in concentrations that imply its local production, and it is argued that its relative concentration reflects a changes in viability and thus integrity of the mesothelial cell layer.[140] Randomized trials of all the normal pH and lower GDP biocompatible solutions have shown that they are associated with a relative increase in the dialysate concentrations of CA 125, implying their greater biocompatibility in vivo and underlining the role GDPs appear to have in adversely affecting mesothelial cell function.[141–143] The benefit appears to be independent of the buffer type used. Other markers that have been investigated include hyaluronan and procollagen peptides, thought to represent interstitial damage or turnover respectively, the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNFα), and vascular endothelial growth factor (VEGF). In each case the biocompatible solutions have been associated with evidence of better preservation of the interstitium, reduced inflammation (IL-6 but not TNFα) and reduced or equal production of VEGF.[137,142,144]

The evidence that use of biocompatible solutions translates into clinical benefits remains less than clear at this stage. The one clear advantage is a reduction in infusion pain associated with bicarbonate-lactate neutral pH solution when compared to either lactate or bicarbonate-only solutions.[26,39] The fact that bicarbonate only solution was associated with more pain that the mixed buffer solution (although still less than lactate only low pH solutions) is of interest. One possible explanation is that supraphysiological concentrations, as are required in a bicarbonate only solution, result in hyperemia of the peritoneal vessels.

Evidence of a clinical benefit on membrane function or preservation of residual renal function is less clear and in some cases contradictory. In part this may be because the available trials are often not comparable as they differ according to which biocompatible component(s) are being compared, for example, buffer, pH, GDP, solution type, and in some cases completely different regimens. Furthermore, some of these studies were not primarily designed or powered with these clinical endpoints in mind. For example, a cross over design is not ideal for investigation of loss of residual renal function. The findings to date are summarized in Table 28-5; if anything, solute transport tends to increase or remain higher with biocompatible solutions,[144–146] and when this occurs, as would be expected, there is a lower ultrafiltration capacity of the membrane.[31,144,146] In these studies where use of biocompatible solutions was associated with less achieved ultrafiltration, the authors have also reported relative preservation of renal function; it is not clear whether this represents a volume effect or a direct effect of the biocompatible solution on kidney function. In those studies with no membrane changes, no change in residual function was found.[147–149] One randomized study of long-term PD patients did report a modest increase in osmotic conductance using biocompatible solution, but this difference was almost significant at baseline.[150]

There are also data supporting better biocompatibility of icodextrin and amino acid solutions when compared to conventional glucose containing fluids. Ex vivo studies of macrophages derived from the effluent following an icodextrin exchange show better phagocytosis compared to those derived from glucose effluent, and mesothelial cells in culture also have better function and viability when exposed to icodextrin rather than glucose,[151–153] although concern has been expressed over the effect of icodextrin on mesothelial cells, albeit less severe that hypertonic glucose.[154] Similarly, amino acid based solutions also show better biocompatibility than glucose solutions, with demonstration in both in vitro and ex vivo

TABLE 28-5 Summary of Trials Comparing Biocompatible with Conventional Solutions Reporting Changes in Membrane Function and Residual Renal Function

AUTHOR, YEAR, REFERENCE	SOLUTION TYPES STUDY DESIGNS	RESIDUAL RENAL FUNCTION	SOLUTE TRANSPORT	ULTRAFILTRATION
Tranaeus, 2000[39]	RCT: Physioneal vs. Dianeal 106 prevalent patients	=	=	↑ (150 ml per day)
Williams, 2004, EuroBalance[144]	RCT, cross over study: Balance vs. StaySafe 71 prevalent patients	↑	↑	↓
Le Poole, 2005[145]	RCT NEPP regime (combines Nutrineal, Physioneal and Extraneal) vs. standard Dianeal 63 incident patients	=	↑	= (UF capacity not known)
Montenegro, 2006[31]	*Non-randomized. Bica Vera* 34 mmol bicarbonate vs. 35 mmol lactate 36 prevalent patients	↑	=	UF capacity in BIC group ↓ from baseline
Szeto, 2007[147]	RCT: Balance vs. StaySafe 50 incident patients	=	=	=
Choi, 2008[150]	RCT: Balance vs. StaySafe 104 prevalent long-term patients (mean 68 months)	=	=	(↑) Already higher at baseline
Kim, 2008, BalNet Study[146]	RCT: Balance vs. StaySafe 91 incident patients	↑ (borderline significant)	↑	↓ Daily UF despite the same glucose load
Fan, 2008[148]	RCT: Physioneal vs. Dianeal and Balance vs. Staysafe 93 incident patients	=	=	=

RCT, Randomized controlled trial.
Increased (↑), decreased (↓), or equivalent (=) to standard solution.

studies improved phagocytosis of macrophage and a reduction in the secretion of inflammatory cytokines, presumably because of lack of glucose or GDP toxicity.[155] Compared to conventional glucose solutions, GDP concentrations in icodextrin and amino acid solutions are significantly reduced, especially in the latter case, such that in both cases single dwell studies show a net loss of AGEs demonstrated by the time-dependant appearance of these compounds into the dialysate effluent, presumably the result of their removal from the circulation or peritoneal membrane.[156] One study evaluating a neutral, bicarbonate compared to lactate buffered amino acid solution suggest that this is more biocompatible.[157] Data awaiting publication would suggest that adverse changes in membrane occurring in anuric APD patients are to some extent ameliorated by use of icodextrin.[158]

Potential Problems

As would be hoped, there are few if any problems associated with the use of more biocompatible solutions (with the exception of specialized solution specific issues discussed previously). Strong evidence for the safety of biocompatible solutions comes from a large, nonrandomized registry study undertaken in Korea. Patients treated with Balance had a significantly better survival, even when corrected for their more favorable baseline characteristics, although disappointingly time to first peritonitis episode or technique failure was not different.[159]

FUTURE DEVELOPMENTS

It can be seen from previous mention that, although significant advances in solution design have been made, there remains room for further improvements. In addition, there is still a lack of evidence that those improvements already made will actually translate into perceived clinical benefit such as improved technique and patient survival rates or better health status/quality of life. A number of potential areas are considered.

Optimization of Ultrafiltration and Sodium Removal

Although the presence of sodium sieving is a good sign in a PD patient, as it is evidence of efficient ultrafiltration induced by small osmolytes through the aquaporin pathway, it results in a potential deficit between sodium and water removal (see Figure 28-1). As discussed previously, this is maximal when a regimen uses short exchanges, such as APD, and may result in worse blood pressure control and [83,84] poor fluid status and contribute to the poor survival seen in APD patients achieving low fluid losses,[48] or with excess use of hypertonic exchanges. This discrepancy between salt and water removal may also explain the increased thirst experienced by PD patients.[160] Optimizing sodium removal is also an attractive way of improving blood pressure control, especially when residual renal function has dropped off. As discussed previously, sodium removal is dependent mainly of convective losses, although diffusion plays a significant part.[40] There are, therefore, essentially two strategies available for increasing sodium loss: increasing ultrafiltration during long exchanges where there is time for the sodium to equilibrate or enhancing diffusion with the use of low sodium dialysate fluids.

Combining a low molecular weight osmolyte (e.g., glucose, glycerol, or amino acid) with icodextrin will increase ultrafiltration that enables sodium to follow as a result of the long dwell time. This approach has already been shown to work,

by combining icodextrin with glucose, to significantly enhance both ultrafiltration and sodium removal.[161,162]

Studies using low sodium dialysates have been performed and also increase sodium removal, although their beneficial effects have been variable, reflecting the difficulties in fluid design.[163–166] Some have reported improvements in blood pressure and echocardiographic parameters, whereas others have observed worrying side effects. A recent exploratory study, investigating two low sodium solutions, found that provided a solution with a 115 mmol sodium concentration was sufficiently compensated with extra glucose (2%) to maintain ultrafiltration that used once a day sodium removal was increased significantly for a given glucose load and associated with improvements in blood pressure, thirst, and fluid status.[167]

Optimizing Biocompatibility

As indicated previously, the evidence that improved biocompatibility of dialysate solutions results in preservation in either preservation of membrane function or the prevention of membrane morphology is keenly awaited. So far the main target of improving long-term biocompatibility has been the creation of low GDP solutions. Further understanding of the mechanisms of how they act and which are important can only enhance this approach. However, at least two other mechanisms (intracellular hypoxia through the sorbitol pathway and non-GDP dependent AGE formation) and probably more of glucose toxicity exist. This invites alternative strategies, and several have been proposed that are either undergoing animal testing or clinical evaluation. These include the use of pyruvate as an alternative buffer,[168,169] glycerol as an alternative low molecular weight osmolyte,[170] or different combinations of existing dialysate fluids during the 24-hour period to achieve a period of glucose free treatment—often referred to a "portfolio" approach.[171]

A Drug Delivery System?

The concept that PD solutions may also act as the vehicle for drug delivery is not a new one. As already mentioned, the delivery of cytotoxic therapy directly to the peritoneal cavity is already being evaluated and used clinically.[172] Antibiotics for the treatment of peritonitis and insulin for the treatment of diabetic patients has been standard therapy for many years. However, more potentially exciting possibilities might be considered in an attempt to preserve or enhance peritoneal membrane function. For example, the intraperitoneal injection of hyaluronan, in an attempt to replace the dialysate losses and thus the integrity of the interstitium, has been performed in experimental animals.[173,174]

A full list of references are available at www.expertconsult.com.

Chapter 29

PERITONEAL DIALYSIS PRESCRIPTION AND ADEQUACY

Peter G. Blake, M.B., F.R.C.P.C., F.R.C.P.I. and Rita S. Suri, M.D.

Since the late 1980s, efforts have been made to apply to peritoneal dialysis (PD) the principles of quantification and prescription of dialytic dose originally established for hemodialysis (HD) by the National Cooperative Dialysis Study and other subsequent publications.[1–3] Over this period, numerous attempts were made to validate this approach by investigating whether measures of small solute clearance are associated with, or are predictive of, patient well-being and survival on PD.[4–6] Initial controversy seemed to have been, at least partly, resolved by large cohort studies from North America and Italy, published in the mid-1990s. These showed a clear association between small solute clearances received and subsequent clinical outcomes, including survival.[7,8] These findings gave rise in a number of countries to influential guidelines proposing relatively high solute clearance targets.[9,10] This, in turn, altered the practice of PD significantly in many jurisdictions.[11,12] However, the publication in the early 2000s of the results of two large randomized, controlled trials looking at the effects of raising clearance has brought into question the validity of this approach in PD and has led to changes in guidelines.[13,14] Analogous results in the large randomized, controlled HEMO trial have led to a similar questioning of the validity of the model in HD.[15] The result is that the whole "*adequacy of dialysis*" field has been in a state of flux.[16]

In this chapter, the standard adequacy indices used in PD will be defined, and the methods by which they are measured will be addressed. The strategies used in clinical practice to raise PD dose will be reviewed. The literature assessing the effectiveness of raising clearance in PD will then be critically evaluated. Special attention will be given to the value of residual renal function (RRF). Evidence-based recommendations will be proposed.

Other aspects of PD adequacy will then be reviewed with particular attention to nutritional factors, management of volume status, and the increasingly emphasized area of glucose sparing strategies in PD patients.

PERITONEAL DIALYSIS ADEQUACY INDICES

Small solute clearance in PD is measured using either urea clearance, normalized to total body water (Kt/V), or creatinine clearance, normalized to body surface area (CrCl). In each case, clearance includes a dialytic and a residual renal component. The latter is particularly important in PD because it accounts for a greater proportion of the overall clearance achieved than is typically the case in HD, and because it appears to persist longer in PD patients.[17,18] It should be remembered, however, that it is only the dialytic component that can be directly modified by the prescribing physician.

The dialytic component is calculated by measuring the urea and creatinine content of a 24-hour collection of dialysate effluent. These values are then divided by the serum urea and creatinine levels, respectively, to give the urea and creatinine clearance (Tables 29-1 and 29-2). Dialysate creatinine levels need to be corrected for the high dialysate glucose content, which interferes with the assay used in many

TABLE 29-1 Formulas Required to Calculate Urea Clearance Normalized to Body Water (Kt/V) and Normalized Protein Equivalent of Nitrogen Appearance (nPNA)

Kt/V

Kt/V per week = 7 (daily peritoneal Kt/V plus daily renal Kt/V)

$$\text{Daily peritoneal Kt} = \frac{\text{24-hr dialysate urea content}}{\text{serum urea}}$$

$$\text{Daily renal Kt} = \frac{\text{24-hr urine urea content}}{\text{serum urea}}$$

According to Watson and colleagues:[19]

V (in males) = 2.447 − 0.09516(A) + 0.1704(H) + 0.3362(W)

V (in females) = −2.097 − 0.1069(H) + 0.02466(W)

where A = age (yr)
H = height (cm)
W = weight (kg)

nPNA

According to Bergstrom and colleagues:[103]

PNA (g/day) = 13 + 7.31 (daily dialysate plus urine urea content*) + daily dialysate plus urine protein content*

or

PNA (g/day) = 19 + 7.62 (daily dialysate plus urine urea content*)

The first formula is preferred because it requires urine and dialysate protein losses to be specifically measured rather than estimated.

$$\text{nPNA} = \frac{\text{PNA}}{\text{standardized or desired body weight (kg)}}$$

*Measured in g/day.
PNA, protein equivalent of nitrogen appearance.

laboratories.[9] The timing of the serum urea and creatinine samples is not important in continuous ambulatory peritoneal dialysis (CAPD) because levels do not vary significantly during the day. In automated peritoneal dialysis (APD), however, there may be a 10% or greater variation in serum urea and creatinine from a trough value after the patient finishes cycling in the morning to a peak value before the patient resumes cycling in the evening. It is thus recommended that serum samples be taken approximately half way through the noncycling period, which, for most patients, means the early afternoon. The renal component of urea and creatinine clearance is calculated in the same manner with a 24-hour urine collection, except that, in the case of creatinine clearance, an average of residual renal urea and creatinine clearance is typically used. This is because unmodified creatinine clearance substantially overestimates the true glomerular filtration rate.[9] The dialysate and residual renal component of clearance are added to give a total clearance, which is normalized to body water (V) to give Kt/V, or to 1.73 m^2 body surface area to give CrCl (see Tables 29-1 and 29-2). The value for V is estimated using anthropometric formulas, such as those of Watson or Hume, based on age, sex, height, and weight.[19,20] Estimates of V from the Watson formulas, when compared to a gold standard, such as deuterium oxide dilution, are, on average, slightly low but the discrepancy varies substantially from patient to patient, especially in the obese.[21] Nevertheless, because most of the clinical literature is based on a V calculated from the Watson equations, and because they have the advantage of simplicity, they remain the current method of choice. In children, the Mellits-Cheek formulas are used.[22] The value for body surface area is similarly estimated using the du Bois formulas.[23] In general, the edema free body weight should be used in the formulas to calculate V and body surface area.[9,10] In the case of patients who have lost a substantial amount of body weight because of malnutrition, it is suggested that the desirable rather than the actual body weight be used in these formulas. This desirable or "normal" body weight can be obtained from the National Health and Nutrition Evaluation Survey tables. These tables give the median body weight of North Americans of the same age, sex, height, and frame as the patient and are regularly updated. It can be argued, however, that they are applicable to a North American population only. The use of the desirable body weight to

TABLE 29-2 Formulas Required to Calculate Creatinine Clearance Normalized to Body Surface Area (CrCl) and Lean Body Mass

$$\text{CrCl} = \text{creatinine clearance} \times \frac{1.73}{\text{body surface area } (m^2)}$$

Creatinine clearance = 7 (daily peritoneal plus daily renal creatinine clearance)

$$\text{Daily peritoneal creatinine clearance} = \frac{\text{24-hr dialysate creatinine content}^*}{\text{serum creatinine}}$$

$$\text{Daily renal creatinine clearance} = \frac{\text{24-hr urine creatinine content}}{\text{serum creatinine} \times 2} + \frac{\text{24-hr urine area content}}{\text{serum urea} \times 2}$$

Body surface area (according to du Bois and colleagues[23]):

Log A = 0.415 Log W + 0.725 Log H + 1.8564

where A = body surface area (cm^2)
H = height (cm)
W = weight (kg)

Lean body mass (kg) (according to Keshaviah and colleagues[25]) = 7.38 + 0.029 (creatinine production [mg/day])

Creatinine production (mg) = Creatinine excretion + creatinine degradation

Creatinine excretion (mg/day) = 24-hr dialysate creatinine* content (mg) Plus 24-hr urine creatinine content (mg)

Creatinine degradation (mg/day) = 0.38 (serum creatinine [mg/dl]) (body weight [kg])

* Corrected for dialysate glucose content by a formula specific to each laboratory.

normalize clearance values avoids the situation where malnourished emaciated patients have a misleadingly high, normalized clearance value and, conversely, one where obese patients have a misleadingly low value. Both Kt/V and CrCl values are conventionally expressed as weekly, rather than daily, clearances to facilitate comparisons with HD.

It has been observed that there is substantial intraindividual variation when repeated clearance measurements are done in the same patient on the same prescription.[24] The variation is particularly marked for the renal component of clearance. Some of this variation may be accounted for by inevitable inaccuracies in collections of dialysate and urine, but some undoubtedly represent genuine day-to-day variation in urinary volume, peritoneal ultrafiltration, and degree of equilibration, consequent upon alterations in hydration, fluid intake, timing of exchanges, and tonicity of peritoneal fluids used.

Dialysate collections may be cumbersome because of the relatively high volumes involved. In CAPD, it is feasible for the patient to bring the entire effluent collection to the clinic. This volume is then measured either in the clinic or in the laboratory, and a representative aliquot is taken for urea and creatinine measurement after appropriate mixing. In the case of APD, the dialysate volumes involved are typically greater. Some centers train patients to record or measure cycler effluent volumes in the home, using the machine reading, and then to take a representative aliquot of the effluent into the clinic for measurement of urea and creatinine levels.

Typically, the residual renal component of clearance declines gradually toward zero over the first 2 to 3 years on PD, but there is great variation. Total clearance will therefore tend to decrease if the dialysis prescription is not modified (Figure 29-1).[25] This was once commonplace, but, as a result of influential publications and guideline recommendations, alterations in the dialytic prescription have become common.

Notwithstanding this, total weekly Kt/V values achieved in PD are typically half to two-thirds of those on HD. This might suggest substantial underdialysis, but it must be remembered that the efficiency, in terms of small solute removal of clearance delivered continuously, is much greater than that of a similar quantity of clearance delivered intermittently.[26,27] Also, continuous modalities avoid the substantial disequilibria of intermittent ones. Furthermore,

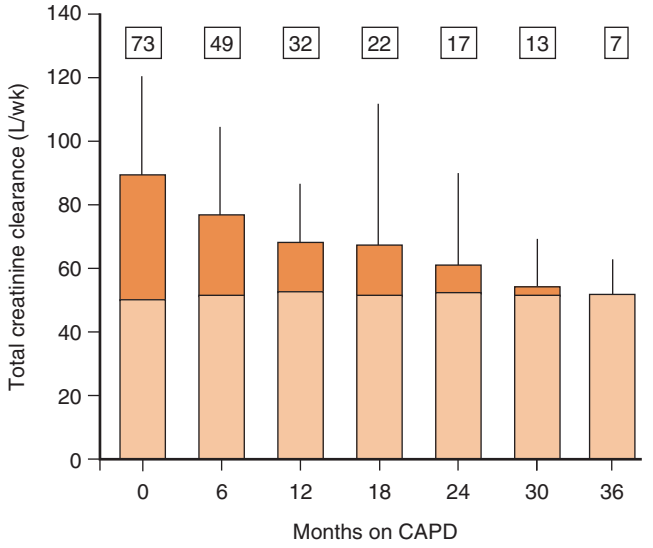


FIGURE 29-1 Changes in clearance with time in standard CAPD. (Modified from P.G. Blake, E.V. Balaskas, S. Izatt, et al., Is total creatinine clearance a good predictor of clinical outcomes in continuous ambulatory dialysis? Perit. Dial. Int. 12 [1992] 353-358.)

continuous modalities may be at a relative advantage because peak levels of uremic toxins are theoretically lower for a given clearance than is the case with intermittent modalities. This concept underlies the "*Peak Concentration Hypothesis*" of Keshaviah and colleagues,[26] which proposes that peak levels rather than mean levels of small solutes are the determinant of uremic toxicity (Figure 29-2). Driven by the increased interest in models of daily HD, as well as PD, a number of investigators have attempted to define indices or methodologies that allow more realistic comparison of intermittently and continuously delivered clearance.[28] None of these has been clearly validated, but there is some evidence that urea clearances, corrected to take into account the frequency of dialytic delivery, are associated with similar patient survival rates. As will be subsequently shown, such indices generally give equal weight to peritoneal and renal clearance, but recent trials suggest that this is not a valid approach.[13,14]

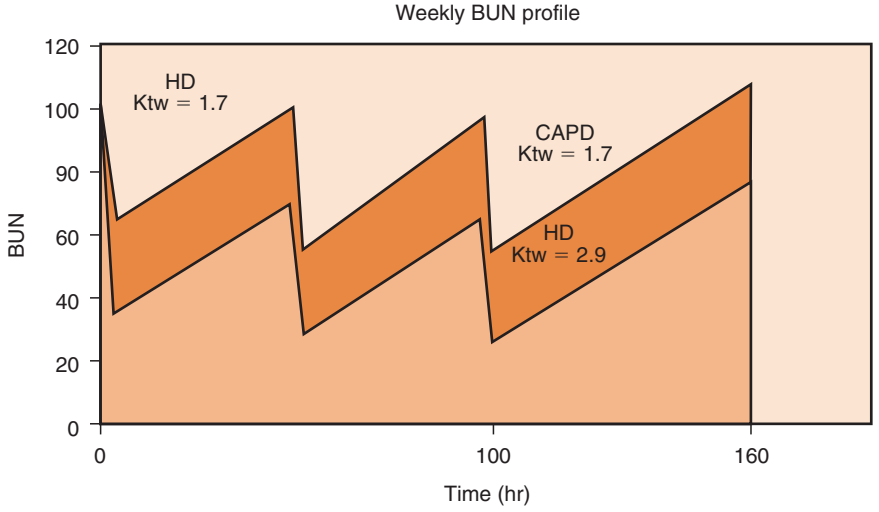


FIGURE 29-2 Peak concentration hypothesis. (Redrawn from P.R. Keshaviah, K.D. Nolph, J.C. Van Stone, The peak concentration hypothesis: a urea kinetic approach to comparing the adequacy of CAPD and hemodialysis, Perit. Dial. Int. 9 [1989] 257-260.)

PERITONEAL EQUILIBRATION TEST

Before discussing peritoneal clearances any further, it is important to have an understanding of the Peritoneal Equilibration Test (PET) and what it measures.[29] The PET is a simple clinical method for assessing the differences in the rapidity with which urea, creatinine, and other solutes diffuse across the peritoneal membrane in different patients. Classically, this involves measurement of dialysate and plasma urea and creatinine levels during a 4-hour duration, 2 L, 2.5% dextrose dwell done under standard conditions. Equilibration curves are constructed based on dialysate to plasma ratios for urea and creatinine, and patients are classified as low, low average, high average, or high transporters with cutoff values being defined by the frequency distribution for the population in the original study by Twardowski (Figure 29-3).[29] Those with values greater than one standard deviation above the mean are classified as high transporters, and those between the mean and one standard deviation above the mean are classified as high average. Those below the mean are classified as low and low average in the same manner. Patients who are high transporters equilibrate quickly and so demonstrate excellent diffusion, but they tend to ultrafiltrate poorly because their osmotic gradient for glucose dissipates relatively rapidly. These patients might be expected to do better with short dwell times as in APD. However, any long duration day dwells may be largely resorbed and so, if one is required, it should be of short duration or, alternatively, be replaced by the polyglucose solution, icodextrin.[30] In contrast, low transporters ultrafiltrate well but equilibrate slowly, and, consequently, large dwell volumes and long dwell times may be more effective. In general, in CAPD patients, urea clearance is much less affected by PET status than is creatinine clearance. This is because a greater than 90% urea equilibration will usually occur, regardless of transport status, with the long dwell times that are typical of CAPD. This is not the case for creatinine equilibration, which may show a twofold to threefold difference between low and high transporters, even after a 4- to 6-hour dwell (see Figure 29-3). In APD, where dwells are typically 1 to 2 hours or less in duration, both urea and creatinine equilibration will vary substantially with PET status, and hence this is a critical determinant of the clearances achieved. As will be seen, this is an important consideration in prescribing APD. Notwithstanding all of this, APD utilization has grown greatly, independent of transport type, and is driven by lifestyle and convenience issues;[31] also, the constraints on achieving clearances in patients with different peritoneal transport characteristics are often not apparent at all until residual renal function is lost.

During the PET, dialysate levels of glucose and sodium may also be measured. For glucose, a graph is presented showing the ratio between the dialysate concentration at 0, 2, and 4 hours as compared to the concentration at 0 hours. The resulting ratio, D/D0 Glucose, is a measure of glucose retention and so is highest in low transporters and lowest in high transporters. For sodium, a D/P graph based on readings at 0, 2, and 4 hours is presented but has an unusual shape. During the first hour when ultrafiltration is greatest, the dialysate falls from its baseline of about 132 mmol/L to a value in the 120s. This is because, when glucose is used as an osmotic agent, approximately 50% of ultrafiltrate generated comes through the aquaporin channels in the peritoneal vascular endothelium, and these allow only water to go through.[32] The result is that the ultrafiltrate contains only half the plasma concentration of sodium and so dialysate sodium falls. However, after about 60 minutes, ultrafiltration is much less and the plasma to dialysate gradient for sodium increases to a point at which significant sodium diffusion can occur. Dialysate sodium levels therefore start to rise back toward 132 mmol/L. The result is a biphasic D/P Na PET curve, reflecting the point that sodium removal is mainly by ultrafiltration in the first half of a 4-hour dwell and is mainly by diffusion in the second half.[32]

CLEARANCES AND OUTCOMES IN PERITONEAL DIALYSIS

Initial studies carried out in the late 1980s and early 1990s to look at the influence of small solute clearance on outcome in PD were small and, in retrospect, methodologically naive.[4,5] Results varied with some showing good correlation between clearance and outcomes and others finding little or no relationship.[4,5,6,33,34] It became apparent in the early studies that, in the context of a relatively uniform CAPD prescription, variations in clearance were due primarily to changes

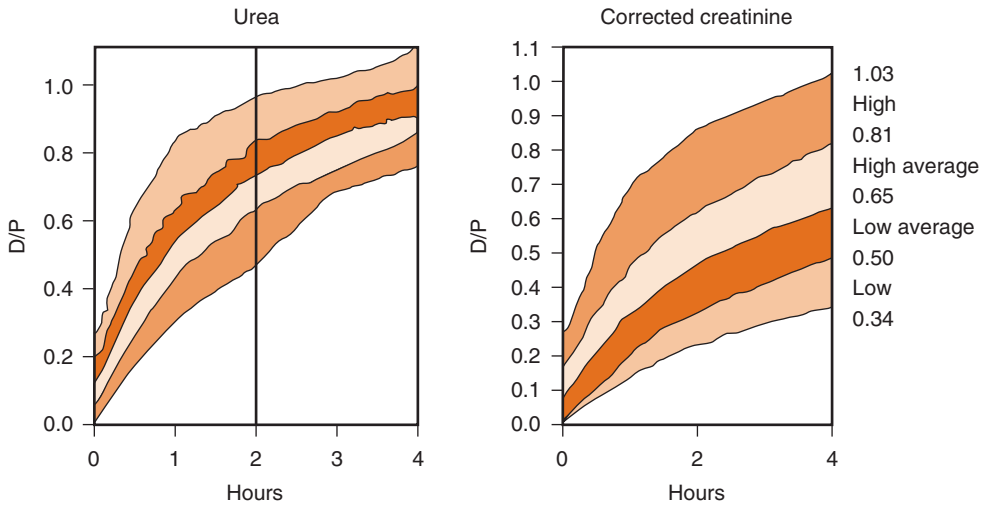


FIGURE 29-3 Peritoneal equilibration curves. (From Z.J. Twardowski, K.D. Nolph, R. Khanna, et al., Peritoneal equilibration test, Perit. Dial. Bull. 7 [1987] 138-147.)

in residual renal function.[4] In subsequent analyses, the need to separate out peritoneal and renal clearance became more evident. In addition, analyses had to take into account the tendency of residual clearance to decline with time, and so frequent remeasurement of clearance indices was required, as were statistical methodologies that attributed outcomes to recent, rather than remote, measurements.

Canada-USA (CANUSA) was a large prospective cohort study of 680 incident CAPD patients done in multiple centers in Canada and in the United States.[7] Follow-up was for 2 years, and the investigators found an impressive association between clearance received and a number of outcomes, including survival. In particular, for every extra 0.1 Kt/V a patient received, the relative risk of dying fell by 6%, and for every extra 5 L a week CrCl, the risk fell by 7%. Maiorca and colleagues[8] found an association between weekly Kt/V values greater than 1.96 and subsequent survival in a cohort of 86 prevalent Italian CAPD patients followed over 3 years. These two studies had a major influence on the U.S. National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) guidelines published in 1997 and revised in 2000.[9] The K/DOQI guidelines recommended a weekly Kt/V of 2 for those on CAPD with modestly higher targets of 2.2 and 2.1 for those on "day dry" APD and on APD with day dwells, respectively. The rationale behind the higher targets for the APD modalities is that they are slightly more intermittent than CAPD and, as already mentioned, intermittency decreases the efficiency of any given amount of delivered clearance.[26–28] The corresponding CrCl targets were 60, 63, and 66 L a week for CAPD, "day dry" APD, and APD with day dwells, respectively.[9]

Criticism of the CANUSA and Maiorca studies and of the consequent DOQI targets focused on the concern that residual function was a severely confounding interpretation of the evidence.[35] The bulk of the variation in delivered clearance in CANUSA was due to declining residual function and not to variations in peritoneal clearance, which was left relatively constant. Neither the CANUSA nor the Maiorca studies were able to show any independent effect of peritoneal clearance on outcome.[36] In a sense, all that was shown was that more residual renal function was associated with superior survival, a not unexpected finding given the associated benefits of native kidney function, such as better volume control, superior preservation of nutritional status, greater middle molecule clearance, and renal endocrine and metabolic function. Clearly, there was a need to show an independent effect of peritoneal clearance on outcome, if the expense and inconvenience of increasing dialytic dose was to be justified. It was clear that randomized, controlled trials were required.

The first two randomized trials addressing this issue appeared in 1997 and 2000 and came from the United Kingdom and Hong Kong, respectively.[37,38] Harty and colleagues[38] used 2:1 randomization of 68 CAPD patients with 42 CAPD patients receiving a 0.5 L increase in their 1.5% dextrose dwell volumes only. Follow-up was for 1 year, but tolerance of the greater volumes was poor with 12 of the 42 not accepting the increase and only 17 completing the year. No difference in survival was identified, but the study was severely underpowered. Mak and colleagues[39] randomized 82 prevalent CAPD patients to 3 × 2 L dwells as compared to 4 × 2 L dwells with 1 year follow-up. Again, there was no difference in survival, but this study was also significantly underpowered.

The ADEMEX study, published in 2002, is the largest randomized trial ever done in PD.[13] Almost 1000 incident and prevalent Mexican PD patients were randomized to receive either the standard 4 × 2 L CAPD prescription or an augmented prescription designed to achieve 60 L per week peritoneal CrCl. This study was well-designed and carried out. Baseline characteristics of the two groups were almost identical, both in terms of demographics, comorbidity, baseline peritoneal clearance, and residual function. This study was large enough to have the power to detect a 20% increase in mortality, equivalent to a 4% absolute difference in 1-year survival. As one would expect, not all of the intervention groups reached the demanding peritoneal clearance target of 60 L a week, but separation between the two groups was substantial (Table 29-3). Survival was identical between the two groups, and furthermore, there was no difference between subgroups, designated by age, sex, diabetes, body size, and presence or absence of residual function (Figure 29-4). This impressively negative study had no major flaws and deals with exactly the range of doses that can be delivered in clinical practice.[11] One objection to the study was the claim that it was carried out in Mexican patients only and might not be applicable to populations elsewhere. In 2003, however, Lo and colleagues[14] reported another large randomized trial comprising 320 incident CAPD patients from six centers in Hong Kong who were randomized to high, normal, and low Kt/V prescriptions of greater than 2, 1.7 to 2, and 1.5 to 1.7 per week, respectively. In this study, the Kt/V target took into account residual function as well as peritoneal clearance, and so the high target was less demanding. The baseline characteristics of the three groups did, unfortunately, vary somewhat in that; for example, the sex distribution, the age, and the body size differed substantially across these groups. Follow-up was 2 years and, again, there was no survival benefit for the high clearance group, as compared to the other two. The low clearance group did a little worse in terms of erythropoietin requirements and study withdrawals, but considering that this was an open-label study makes the latter finding hard to interpret.[14] Overall, the Lo study appeared to support the ADEMEX finding that high clearance PD prescriptions do not improve outcomes.

Another criticism of ADEMEX, and implicitly of the Lo study, was that both comprised populations with relatively lower rates of cardiovascular disease as compared to those seen in North America and Western Europe.[39,40] In the case of ADEMEX, patients with overt cardiac disease were excluded, and in Hong Kong the prevalence of this

TABLE 29-3 Weekly Kt/V and CrCl Values in ADEMEX

	STANDARD GROUP	HIGH CLEARANCE GROUP
Peritoneal Kt/V	1.62	2.13
Total Kt/V	1.8	2.27
Peritoneal CrCl	46 L	57 L
Total CrCl	53 L	63 L

CrCl, creatinine clearance, normalized to body surface area; *Kt/V*, urea clearance, normalized to body water.

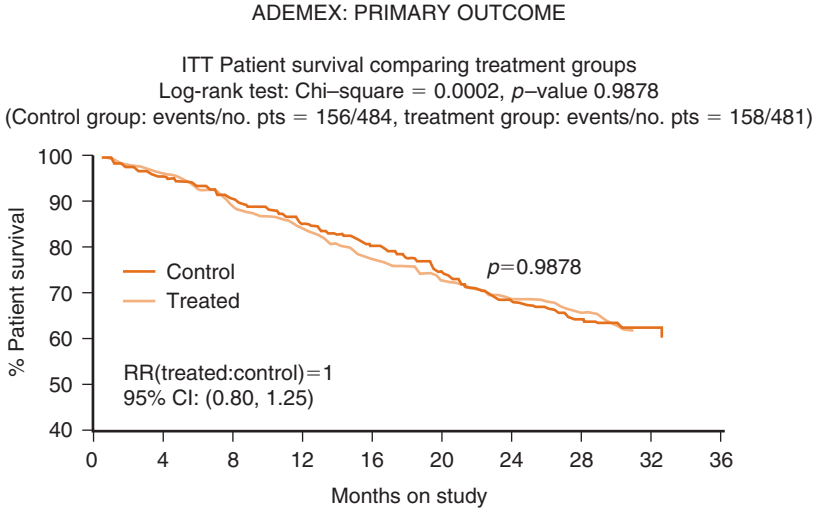


FIGURE 29-4 Survival in ADEMEX study. (From R. Paniagua, D. Amato, E. Vonesh, et al., Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial, J. Am. Soc. Nephrol. 13 [2002] 1307-1320.)

complication in PD patients is relatively low to begin with. However, 60% of deaths in the ADEMEX study were cardiovascular in etiology, and this did not differ between the two groups. Another concern relates to the possibility of noncompliance in the intervention groups in these studies. This is always an issue in any study, or real-life situation, that requires the patient to deliver a treatment. Analyses based on blood work from ADEMEX, however, suggest that the extra dialytic dose was generally delivered. An additional issue raised regarding ADEMEX was the finding that, although the absolute number of deaths did not differ across the two groups, those attributed to congestive heart failure and uremia, hyperkalemia, and acidosis were significantly more frequent in the control group. Similarly, there were more dropouts attributed to uremia in the control group. Overinterpretation of these findings should be avoided, however. ADEMEX was, by its nature, an open-label study, and there is a strong possibility that physicians classifying the etiology of deaths and withdrawals from the study would be more likely to designate those in the control group as being the result of uremia or volume overload.

Residual skepticism about ADEMEX should also be tempered because the findings do not differ from those of the CANUSA[7] and of Rocco and colleagues'[12] studies. Each of these studies, a randomized, controlled trial, a prospective cohort study, and a retrospective analysis, respectively, showed a very similar effect of residual renal function on survival, and each showed no effect of peritoneal clearance (Table 29-4). There is a convincing consistency about these findings. Accordingly, apart from some reservations about unreservedly applying the results to patients with overt cardiac disease, it would be unreasonable to not accept the findings of ADEMEX and of Lo and colleagues as valid and highly relevant. A broad consensus on this reflected in the reductions made in clearance targets by various guideline groups, including K/DOQI, in recent years.

NEW RECOMMENDATIONS

After these randomized trials, NKF K/DOQI, the European Renal Association, and the International Society of Peritoneal Dialysis (ISPD) all published new clearance guidelines. Each chose a weekly target Kt/V of 1.7 because this is the dialytic dose received by the control group in the ADEMEX study, with a modest increment added for safety.[13,40–43] K/DOQI recommended that CrCl no longer needed to be measured because there was no evidence that it added anything to Kt/V, and having one clearance index only had the attraction of simplicity.

Both the ISPD and European guidelines retained CrCl targets of 50 and 45 L/wk, respectively, in the belief that uremic toxins may have higher molecular weights than urea, and ignoring this might lead to underdialysis in low transporters, especially on APD. This belief is based on faith rather than evidence, however. All of the newer guidelines did away with the concept of different Kt/V targets for CAPD and APD because both of these PD modalities are

TABLE 29-4 Relative Risks for Mortality by Peritoneal and Renal Clearance Indices in Three Major Studies

	CANUSA	ROCCO AND COLLEAGUES	ADEMEX
TYPE OF STUDY	**PROSPECTIVE COHORT**	**RETROSPECTIVE ANALYSIS**	**RANDOMIZED TRIAL**
Peritoneal CrCl	1.04 (ns)	0.9 (ns)	1.03 (ns)
Renal CrCl	0.83 (p = 0.001)	0.6 (p <0.001)	0.89 (p = 0.013)
Peritoneal Kt/V	1.00 (ns)	1 (ns)	1 (ns)
Renal Kt/V	0.68 (p <0.001)	0.88 (p = 0.003)	0.94 (p = 0.005)

ns, not significant.

(Adapted from Canada-USA [CANUSA] Peritoneal Dialysis Study Group, Adequacy of dialysis in nutrition in continuous peritoneal dialysis: Association with clinical outcomes, J. Am. Soc. Nephrol. 7 [1996] 198-207; M. Rocco, J.M. Souci, S. Pastan, et al., Peritoneal dialysis adequacy and risk of death, Kidney Int. 58 [2000] 446-457; and R. Paniagua, D. Amato, E. Vonesh, et al., Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial, J. Am. Soc. Nephrol. 13 [2002] 1307-1320.)

relatively continuous, compared to three times weekly HD, for example. There is also no convincing need for different targets by transport type either, especially when CrCl is taken out of consideration.

A target Kt/V value of 1.7 peritoneal is, with a bit of effort, feasible in almost all patients. In most, it will not require prescriptions that unreasonably disrupt the already impaired quality of life of dialysis patients.

Even though a given amount of residual renal and the same amount of peritoneal urea clearance clearly do not have the same value in terms of predicting survival, the guidelines continue to advocate adding these together. This allows some degree of "*incremental*" *or* "*early start*" PD to be practiced with patients being initiated on dialysis while residual function is still substantial. In such cases, it gives a justification for a lower peritoneal prescription, such as two to three CAPD exchanges daily or "day dry," low-volume APD.[39] However, incremental PD should only be practiced in units that frequently monitor residual renal function.

Trials of higher peritoneal Kt/V clearances than 1.7 per week might still be indicated if patients have persisting uremic type symptoms, and, particularly, if there is coexisting cardiovascular disease, but expectations for a beneficial effect would have to be guarded and alternative diagnoses and treatments considered.

WHY DO HIGHER CLEARANCES NOT HELP?

Why is high clearance PD not more successful in improving quality and quantity of life? Similar questions are being asked about high clearance HD in the aftermath of the equally negative HEMO study. A number of possible answers need to be considered.[16]

One is that relative to the clearance provided by normal kidneys, the levels being tested in these trials are very low. Comparisons of 4 to 6 ml as compared to 6 to 8 ml a minute, as was done in ADEMEX, seem very modest if 60 ml/min or more is considered to be normal. Proponents of this point of view argue that dialysis will significantly improve survival only if substantially greater clearances are delivered, as might be the case with daily or nocturnal HD.[45] An alternative view is that survival in end-stage renal disease (ESRD) is primarily determined by associated comorbidity and not by variations in dialytic dose. Once frank uremia is prevented by a baseline amount of dialysis, incremental survival requires not more clearance but rather a more successful strategy for preventing and treating cardiovascular disease and infection, the two great killers of dialysis patients.[16]

Others still argue that the small solute clearance is the wrong "yardstick" and that middle molecule clearance has been neglected or that indices of volume control may be more important. These theories may be correct, but the HEMO study gives little support to the middle molecule hypothesis, and no new dogma should be accepted unreservedly without more convincing proof.[15]

Last, the notion that high clearance PD is doing no harm and that patients should therefore be given "the benefit of the doubt" also needs to be addressed. Not only is high-dose PD more costly, but it is also potentially onerous for patients.[46] Larger dwell volumes in the ADEMEX and other studies were associated with mechanical symptoms leading to dropout, hernias, and so forth.[13] More exchanges may increase the risk of peritonitis, and there is evidence that patient noncompliance also results.[47] Cycler prescriptions with 2, 3, or more day dwells may also impair quality of life. Furthermore, increases in dialytic dose generally lead to more peritoneal glucose exposure and absorption, and there is a growing body of evidence that this is deleterious, not only to the peritoneal membrane but also, more critically, to the patient's cardiovascular risk profile.[48,49]

STRATEGIES TO INCREASE PERITONEAL CLEARANCE

Notwithstanding recent skepticism concerning the benefits of augmented PD prescriptions, it will still be necessary to prescribe more than the conventional 4 × 2 L CAPD or 10 L per night APD regimens to bring some patients above the proposed 1.7 peritoneal Kt/V target.[50]

In CAPD, an increase in dwell volume from 2 to 2.5 L is the least disruptive approach, is usually well-tolerated, and leads to approximately a 20% increase in peritoneal clearance.[50] The need to use 3-L volumes is less with these lower Kt/V targets. The alternative strategy of adding a fifth exchange is less attractive because it is more expensive and disruptive of lifestyle and because it is associated with increased noncompliance.[46,47]

APD is increasingly the chosen option for PD patients.[11,31] The addition of a day dwell is the most effective way to increase clearances with this modality. This is particularly so in the patient who is "day dry," where the resulting increase in clearance is often 30% to 35%.[50] If a day dwell is already being used, the addition of a second one will also have a substantial effect, provided that each is in place for at least 4 hours to allow good solute equilibration. Strategies based on using the cycler as a "*docking station*" reduce the cost and inconvenience of adding a second day dwell, although they do require the patient to return to the cycler to do the exchange.[51] A manual "*double bag*" exchange is an alternative for the patient who does not wish to return to the cycler. If there is just 1 long day dwell, fluid resorption may be a problem. In this situation, an early drain after 4 to 8 hours may be an option that increases ultrafiltration, preserves clearance, and even enhances lifestyle in that many patients prefer being "empty" for at least some of the day. An alternative approach to maintaining ultrafiltration is to introduce the polyglucose solution, icodextrin, for the long day dwell.[30] This approach is also useful for the long nocturnal dwell in CAPD.

Alternative methods of raising clearance in APD are to increase the number of cycles per treatment session. Typically, this effect starts to plateau out once the number of cycles exceeds about seven per 9-hour cycling session.[50,52,53] This number may be a little higher for high transporters, but the cost of more than seven cycles per night is also a factor.[46] Also, such an approach may decrease sodium removal and increase glucose exposure and absorption. Lengthening the cycler time is also somewhat effective in increasing clearance, but, again, there are lifestyle constraints. Larger dwell volumes may also help; that is, 4 × 2.5 L give better clearance than 5 × 2 L. The effect is modest, and some argue

that the rise in intraperitoneal pressures with higher volumes may impair ultrafiltration.[54]

An additional consideration when prescribing APD is the phenomenon of sodium sieving described in the previous section on peritoneal equilibration testing. The consequence of this is that sodium removal is disproportionately less, relative to water removal, in APD compared to CAPD because the short dwell times leave less time for sodium diffusion to compensate for the ultrafiltration-induced sieving that occurs early in the dwell.[32] This effect is more pronounced when high frequency cycling is used. So, in patients in whom salt removal is especially important, high frequency cycling is best avoided.

Measurement of peritoneal clearance should be carried out once the new PD patient stabilizes on the initial prescription. It is best to remeasure clearance every 6 months, as part of a general check on the prescription that the patient is doing.[9,10] Measurement should also be repeated soon after any prescription change and in the event of any unexplained change in clinical status. Residual renal and urinary volume should be measured at the same time as peritoneal clearance. However, if the patient is on an "*incremental*" PD prescription with an initial low peritoneal clearance, residual renal clearance should be measured at 2-month intervals to avoid missing a decline in residual function and consequent underdialysis.[44]

MAINTENANCE OF RESIDUAL RENAL FUNCTION

One lesson that PD practitioners have learned in the past decade is the impressive value of preservation of even very modest amounts of residual renal function. Thus, in the CANUSA study, an extra 5 L a week creatinine clearance, which is equivalent to 0.5 ml/min glomerular filtration rate, was associated with a 7% increase in survival.[7] Similarly, a 250-ml increment in urine volume was associated with a 36% decrease in relative risk of death. When renal clearance and urine volume were added to the same Cox model, the urinary volume appeared to be the stronger predictor of survival.[36] Other studies have shown that RRF is a crucial factor in the maintenance of good volume, cardiac status, and control of hyperphosphatemia and that it may also decrease the risk of malnutrition.[55–57]

Of course, all of these may not be cause and effect. It is plausible that preserved renal function may be a marker of general well-being, of less systemic inflammation, or just of an earlier stage in the evolution of ESRD.[58] However, the possibility that better preserved function enhances survival through its effects on volume status, middle molecule clearance, metabolism, or nutrition is also quite plausible.

The preservation of residual function would therefore seem to be a priority. A randomized, controlled trial has shown that angiotensin-converting enzyme (ACE) inhibition and, in particular, ramipril 5 mg daily, was associated with better retention of residual function and lower probability of anuria.[59] This study, based on 60 CAPD patients in Hong Kong, with no other indication to be on an angiotensin converting inhibitor, showed a small but significant effect with a 1 ml/min greater clearance at 12 months and a 42% lower chance of development of anuria. A similar randomized study by Suzuki and colleagues[60] showed analogous benefits for the angiotensin receptor blocker, valsartan.

In another randomized, controlled trial, Medcalf and colleagues[61] randomized 61 incident PD patients to either furosemide 250 mg/day or no diuretic. Urine volume was better maintained at 1 year in the furosemide group with a difference of just over 350 ml/day. Urine sodium excretion was also enhanced, and volume status appeared better in that percentage of body water measured by bioimpedance rose in the control group but stayed constant in the treatment group.

ACE inhibitors and high-dose furosemide appear to be safe interventions in PD patients, and this evidence that they are reasonably effective in maintaining urinary clearance and volume, respectively, would appear to justify their routine use. Other strategies to consider in preserving residual renal function are to avoid, as much as possible, volume depletion, the use of aminoglycosides, nonsteroidal antiinflammatories, and radiological contrast. When the latter has to be used, renoprotection with intravenous saline and administration of acetylcysteine should be considered, if residual renal function is still significant.[62] Early suggestions that new PD solutions with more physiological pH and lower levels of glucose degradation products would be renoprotective have not been borne out by randomized trials.[63] There is also little evidence that icodextrin has such a benefit.

NUTRITION

The influence of nutrition on outcomes and survival in dialysis patients has long been appreciated. A variety of nutritional indices predict survival in PD patients. These include serum albumin, subjective global assessment, lean body mass, and other indices of creatinine production, total body nitrogen, a variety of other composite nutritional indices, and, in some studies, protein intake.[7,8,64–66]

The mechanism of this association of nutrition and survival is not clear. A crucial issue is whether it represents cause and effect or just association. In other words, is the poor nutrition the proximate cause of the inferior outcomes, or are they both common consequences of underlying comorbid conditions that are the true cause of the patients' poor survival? Traditionally, nutrition and clearances have been linked together with the theory being that inadequate clearances lead to poor protein intake, which, in turn, leads to malnutrition and premature death.[13] This idea stems from the general observation that degree of uremia and appetite for protein are closely correlated and also from the suggestion in the 1980s that Kt/V and protein intake were closely associated.[67] However, this paradigm has been shown to be an oversimplification. The original observations relating clearance and protein intake were confounded by the phenomenon of "*mathematical coupling*."[68,69] More significantly, there is now a greater awareness that much of the malnutrition seen in dialysis patients is independent of dialytic dose.[70,71]

Contributors to impaired nutritional status in PD patients can be divided into those that are found in ESRD in general and those that are specific to PD (Table 29-5). The former include inflammation, metabolic acidosis, impaired protein anabolism, uremic anorexia, and the contribution of associated comorbidities. The latter include the obligatory dialysate protein losses, some of the impairment of gastric emptying, and the effects of any peritonitis episodes suffered by the patient.

TABLE 29-5 Factors Contributing to Malnutrition in PD Patients

GENERAL ESRD-RELATED CAUSES	PD SPECIFIC CAUSES
Uremic anorexia	Dialysate protein losses
Inadequate dialysis	Impaired gastric emptying (present in ESRD but worse in PD)
Systemic inflammation	
General comorbidity	
Gastrointestinal comorbidity (e.g., gastritis, ulcers, constipation, diabetic gastropathy)	Anorexic effect of dialysis glucose absorption
	Peritonitis episodes
Metabolic acidosis	
Growth hormone resistance	
IGF-I resistance	
Medication side effects (e.g., oral iron, phosphate binders)	
Socioeconomic deprivation	
Poor dietary habits (e.g., previous low-protein diets)	
Decreased activity	
Depression	

The greatest area of interest, in the past decade, with regard to the etiology of malnutrition in renal failure has been in the notion that persistent inflammation is a critical underlying factor. Inflammation, as indicated by elevated serum C-reactive protein (CRP) and interleukin-6 levels, is present, usually without any clinically obvious cause, in as many as 30% to 60% of dialysis patients.[71–74] Most importantly, it is associated with decreased survival in ESRD patients. It has been associated in some studies with progressive atherosclerosis, giving rise to the concept of the "*malnutrition inflammation atherosclerosis*," (MIA) syndrome.[71,75] Inflammation has also been shown to account for much of the hypoalbuminemia seen in both PD and HD patients, an effect mediated through decreased hepatic albumin production, consequent on a chronically "turned on" acute phase response.[76]

Why ESRD patients should have chronically stimulated immune responses is unclear. Initial theories proposed a role for the bioincompatible aspects of dialysis, such as the blood membrane interaction in hemodialysis and the dialysis solution peritoneal membrane interaction in PD.[71–73] However, the finding that inflammation is equally common in patients with advanced renal failure before initiation of dialysis argues against this being the major cause.[73] Another possibility is that the inflammation is directly related to renal failure per se and the associated impaired clearance of cytokines.[77] However, there is no clear proportionality between clearances and inflammation, and so this cannot be more than a modest part of the overall explanation. Coexistent comorbid conditions, in particular, cardiovascular disease, may be a critical player in cytokine activation, although which is the cause and which is the consequence are unknown.

Management of the inflammation of ESRD has not been very successful. The cardiology literature varyingly suggests roles for statins, aspirin, and even ACE inhibitors in suppressing inflammation, but there is little evidence as to how effective these strategies are in ESRD.[78–82]

Numerous studies in recent years testify to the contributory role of acidosis to the impaired nutritional status of renal failure.[83–85] The mechanism here is increased breakdown of muscle protein due to activation of the ubiquitin-proteasome proteolytic system.[84,85] In PD patients, acidosis tends to be less of an issue because the continuous nature of the dialysis usually ensures good maintenance of serum bicarbonate.[86] Two randomized trials have shown that supplementation to increase the serum bicarbonate to levels that are in the high normal to alkalotic range improves nutritional parameters modestly and decreases hospitalization in PD patients.[87,88] Oral sodium bicarbonate should therefore be considered in the minority of PD patients with a serum bicarbonate level less than 25 mmol/L. More aggressive use of bicarbonate is probably not justified by the available data. The introduction of bicarbonate based PD solutions has only a very mild effect on serum bicarbonate levels.[89]

Another important factor in the malnutrition of ESRD is impaired anabolism. The etiology of this relates to uremia being a state of resistance to a number of hormones involved in nutrition and metabolism, most notably insulin, growth hormone (GH), and insulin like growth factor one (IGF-I).[90–92] The etiology of this state of resistance is complex and multifactorial. Some theories have implicated high levels of GH and IGF binding proteins or abnormalities of GH and IGF receptors, whereas others focus on post receptor mechanisms.[90–92] Whatever the etiology, the consequence of this is that nitrogen supplements are frequently not effectively anabolized in renal failure and may just result in increased levels of blood urea. Strategies to deal with this include administration of recombinant GH and recombinant IGF-I.[92–94] These approaches are, however, constrained by concerns about side effects and cost. A major randomized trial that had been undertaken to look at the role of GH in hemodialysis patients, however, was abandoned secondary to a slow pace of recruitment.[95] An alternative approach is to use anabolic steroids such as nandrolone. Johansen and colleagues[96] reported in a small randomized trial of 29 HD and PD patients that this agent given for 6 months at a dose of 100 mg weekly was associated with increases in muscle mass and, more significantly, with improvements in functional performance. A subsequent trial done in only HD patients showed a less convincing benefit, and the strategy is not widely used but deserves consideration.[97]

Obligatory protein losses in PD average 8 to 9 g/day, about half of which is accounted for by albumin.[98] This is the primary cause of the hypoalbuminemia seen in PD patients.[64,76,99] Protein losses increase in the presence of peritonitis and generally tend to be greater in those with high transport status.[64,76] Losses are not generally influenced by dialysate flow rates, but they may be less in patients who are left "dry" for part of the day. No convincing method of decreasing dialysate protein losses has been identified.

Suboptimal protein intake is a frequent feature in PD patients.[7,13] The widely quoted protein intake PNA target of 1.2 g/kg body weight/day is based on observations made in younger, healthier patients than those typically seen in contemporary PD programs.[100] Even more modest targets of 0.9 to 1 g/kg/day are often not achieved.[101] Some of this reflects the decreased activity, the comorbidity, and the general poor health of many patients. However, an additional factor is the impaired gastric emptying seen in many PD

patients.[102,103] This is more marked in diabetics and seems, at least in part, to be related to the dialysate glucose content.[102]

DIAGNOSIS OF MALNUTRITION

High awareness of the frequency and significance of malnutrition is important. Basic history taking and clinical examination with assessment of food intake, appetite, weight, fat stores, and muscle mass should be routine practice in the evaluation of PD patients. Some of this can be formalized in the technique of subjective global assessment.[7] Regular evaluations by a experienced dietitian are also important with particular regard to assessment of nutrient intake. Low serum levels of urea, potassium, and phosphate are all suggestive of poor intake. Urea kinetics can be used to estimate the normalized protein equivalent of nitrogen appearance (nPNA), a surrogate for protein intake in a stable patient. The rationale here is that urea generation and excretion in the stable patient is proportional, in a predictable manner, to protein intake. A variety of formulas have been used to estimate protein intake from urea and other nitrogen losses. Some are taken from the chronic renal failure or hemodialysis literature, whereas others were derived directly from PD patients (see Table 29-2).[101,104,105] The best validated are those of Bergstrom.[106] Normalization of the calculated protein intake is typically done using desirable rather than actual body weight because the latter can be misleading if there is marked malnutrition or obesity.[9,10,107] Desirable body weight can be taken from standardized tables based on age, sex, height, and body frame. Simple estimates of body composition can be performed using creatinine excretion in dialysate and urine to estimate lean body mass.[108] Formulas for this take into account extrarenal creatinine degradation as well as level of serum creatinine. Estimates based on these measurements have been shown to be predictive of outcomes.[7,65] More sophisticated methods of assessing body composition include bioelectric impedance, DEXA, and total body nitrogen measurements.[66,109,110]

Serum albumin is now recognized to be a poor measure of nutrient intake in the PD patient but a low value, along with a high CRP level, may be a clue to ongoing inflammation.[76] The other major contributor to hypoalbuminemia in this setting is high peritoneal transport status and the associated dialysate protein losses.[64,99]

MANAGEMENT OF MALNUTRITION

Malnutrition is a frustrating complication of ESRD because it is frequently not amenable to correction. A multidisciplinary approach is preferred involving the dietitian, the nurse, the social worker, and the physician.[9,10] Attention to social, economic, and educational factors is important. Medications should be reviewed, looking particularly at those, such as oral iron, phosphate binders, and nonsteroidal antiinflammatories, which may be irritating to the stomach. Comorbidities, such as poor dentition, gastrointestinal disease, and depression should be looked for and addressed. Counseling concerning the importance of protein intake is essential, but frequently patients cannot achieve the recommended targets of 1 to 1.2 g/kg/day, and, in these situations, it is important that more modest increments be encouraged.[9,10] Indeed, there is evidence that patients can go into nitrogen balance at lower levels of protein intake.[101]

Identification and correction of underdialysis is an important aspect of managing malnutrition, but as already mentioned, this is now understood to be a less significant contributor than was thought to be the case in the past. However, peritoneal Kt/V values less than 1.7 in the presence of malnutrition should be considered an indication for increasing clearance. Oral sodium bicarbonate supplements should also be considered if the serum bicarbonate is low.[87,88] If symptoms are suggestive of impaired gastric emptying, a trial of a promotility agent, such as domperidone, should be considered.[103] There may also be a role for empirical use of antacid agents, such as protein pump inhibitors or histamine antagonists. Identification and treatment of *Helicobacter pylori* infection may also help.[111] If elevated serum CRP levels indicate the presence of inflammation, a search for a primary cause may be made, but a specific treatable entity is uncommonly identified and, more often, there is nothing definitive or just generalized comorbidity.[73]

Trials of protein and/or nitrogen supplements are commonly carried out even though there is little evidence that this approach is effective in improving clinical outcomes in ESRD patients. Randomized trials looking at oral supplements have not shown impressive results.[112–114] Patient tolerance for some of these supplements is limited, and evidence of improved outcomes is scant. If oral supplements are not of benefit, consideration should be given to using intraperitoneal amino acids. Modest benefits have been demonstrated for these in clinical trials.[115–117] They have been shown to improve nitrogen balance and, in some studies, to induce an anabolic response and to ameliorate hypoalbuminemia. The best and longest randomized trial followed 60 patients over 3 years and showed better preservation of muscle mass and of serum albumin in the treated group, but the study was too small to look at more important outcomes such as mortality.[117] Intraperitoneal amino acids may induce uremia or acidosis and so caution should be used in prescribing. For this reason, use is limited to one bag of 1.1% amino acids daily, given at the same time as ingestion of an energy source. Recently, administration via the cycler, in association with glucose to improve their anabolism has been proposed with some supportive data. Overall, given the risks of acidosis and uremia, the extra cost, and the modest benefits shown, intraperitoneal acids are not widely prescribed.[118]

Feeding by gastrostomy tube has occasionally been attempted in adults with ESRD but is more frequently done in children. This intervention can be successfully carried out in patients on PD, but complications are significant, and, again, there is little evidence of long-term benefit.[119]

Approaches based on improving anabolism have also been studied. One randomized trial done in both HD and PD patients showed benefits for the use of anabolic steroids.[96] This trial was small but still showed important functional improvements in the patients receiving the intervention. The anabolic effects of recombinant GH and of IGF-I have also been demonstrated in a number of studies, but their use is not practical in view of concerns about side effects and high costs.[93,94]

If all of these approaches are ineffective and the patient is clinically failing, a trial of HD may be worth considering. Some patients improve after such a switch, but there is often no change.

VOLUME STATUS IN PERITONEAL DIALYSIS

The importance of achieving optimal volume status in both PD and HD patients has been emphasized recently for a number of reasons. First, the failure of an approach based on small solute clearance to reduce ESRD mortality substantially has encouraged investigators to look at other approaches to improving outcomes.[13,14,16] Second, the increasing realization that dialysis, as presently practiced, is not normalizing blood pressure in most patients has caused concern, given that cardiovascular disease is the commonest cause of death in these patients.[120,121] The notion that hypertension usually reflects inadequately managed volume status and may be contributing to adverse cardiovascular outcomes has therefore become popular.[121,122]

In PD patients, there is some evidence that volume status is even less well-controlled than in HD patients.[123,124] This is most likely to be the case after residual renal function is lost.[57,125]

Much of the literature on fluid overload in PD deals with the differential diagnosis of problems with the peritoneal membrane for which the term "*ultrafiltration failure*" (UFF) is commonly used. However, it should be emphasized that UFF is not the only cause of fluid overload in PD patients. Indeed, in the early years of PD, UFF is relatively uncommon and other causes should be sought.[125]

Nonmembrane causes of fluid overload are shown in Table 29-6. Excess salt and water intake and declining urine output are often major contributing factors. In some patients, noncompliance with the PD exchanges or inappropriate selection of dialysis solution strengths contributes to the problem. Mechanical complications that impair peritoneal fluid drainage may also be an issue. These lead to greater residual volumes and consequent fluid resorption. Examples include poorly functioning catheters, peritoneal leaks, loculations in the peritoneal cavity, and even hernias. More recently, retroperitoneal dialysate leaks have been described as a not uncommon cause of impaired ultrafiltration.[126] Hyperglycemia may also contribute by decreasing the glucose osmotic gradient driving ultrafiltration.[125]

Careful history taking, physical examination, and inspection of dialysis records should help identify these nonmembrane causes of UFF. In some situations, direct observation of dialysate drainage, assessment of residual volume, and contrast peritoneography may be helpful.[125]

TABLE 29-6 Causes of Fluid Overload

MEMBRANE CAUSES	NONMEMBRANE CAUSES
Type I—high effective membrane area	Excess salt and water intake
Type II—inadequate effective membrane area	Marked decline in urine output
Type III—excessive peritoneal fluid absorption	Noncompliance with PD prescriptions
	Inappropriate choice of solution tonicity
Other types—impaired aquaporin function	Peritoneal leak (abdominal wall, retroperitoneum, perineum)
Impaired hydraulic conductance	Poor catheter function with resulting high residual volume
	Hyperglycemia inadequate osmotic gradient

ULTRAFILTRATION FAILURE

UFF is best used to refer to cases of clinical fluid overload in which membrane dysfunction is identified as the primary cause of the problem. The classic definition is a net ultrafiltration volume of less than 400 ml at the end of the standard 2-L, 4-hour duration 4.25% dextrose dwell.[127]

The commonest cause of this, known as type I UFF, is where equilibration across the membrane is so rapid that the osmotic gradient for glucose dissipates before adequate ultrafiltration has had time to occur. Rapid transport status is present from the initiation of PD in a minority of patients, whereas, in others, it appears with time. Thus the cumulative incidence of UFF in one study was 2.6% after 1 year on PD, rising to 9.5% after 2 years, and to 30.9% after 6 years.[128] This cumulative rise in incidence is partly related to the tendency for peritoneal transport to increase significantly in many patients. It is, however, frequently made more overt by the simultaneous tendency to lose residual renal function over the same time course.

The causes of the increase in peritoneal transport that tend to occur with time have been a focus of research interest. Pathologically, there is an association of decreased ultrafiltration with submesothelial fibrosis, vasculopathic changes, and neovascularization.[129] The latter is believed to be the most significant finding in that vascular proliferation increases the effective peritoneal surface area and so results in more rapid transport.

The most popular hypothesis is that exposure to hypertonic glucose is the key factor in this process. Analogous pathological and functional changes occur in diabetic animal models. There is a plausible pathway by which glucose and glucose degradation products (GDPs) in PD solution induce vascular endothelial growth factor (VEGF), which, in turn, promotes neovascularization through the action of nitric oxide.[130,131] De Vriese and colleagues[132] have, for example, shown that anti-VEGF antibodies can prevent much of the deterioration of ultrafiltration in animal models of PD.

Recently, Davies and colleagues[43] have strengthened this glucose related hypothesis by showing that patients who develop increased transport characteristics tend to have been exposed to more hypertonic glucose exchanges in their early years on PD, as compared to other patients who maintain relatively stable membrane transport. Glucose exposure may not be the only factor, however. The Davies study also found that patients with stable peritoneal transport were more likely to have maintained their residual renal function for longer.[48] This may be association or it may be cause and effect. It is possible that some factor associated with residual renal function is protective for the peritoneal membrane. Chung and colleagues[133] have speculated that systemic

inflammation might be such a factor. As previously discussed, systemic activation of cytokines can be detected in approximately half of all PD patients. Chung and colleagues[133] have shown that these patients are more likely to show increases in peritoneal transport in the first year on PD. The same patients are more likely to show faster declines in residual renal function.[58] The evidence for this hypothesis is as yet not as strong as for the dialysate glucose mechanism.

Other bioincompatible features of PD solutions may contribute to peritoneal membrane damage. The glucose degradation products that arise during glucose sterilization may, in addition to stimulating VEGF production, also give rise to advanced glycosylation end products, which may themselves damage membrane function.[130,131] Other potential PD solution-related factors include low pH and lactate. Evidence for these is less convincing. The contribution of cumulative episodes of peritonitis to membrane function is relatively controversial with different studies yielding contrasting results.[134] The consensus at this stage is that mild peritonitis causes little permanent damage to the membrane, but severe peritonitis may be a contributor.

Type II UFF is much less common. In this condition, peritoneal transport of small solute and of water actually decreases. This reflects a loss of peritoneal surface area. Most often, this is seen in the context of peritoneal adhesions acquired during severe peritonitis or after surgical complications. The available surface area for dialysis is too small and neither solute nor water transport is adequate. Some investigators have proposed that type II UFF may be a harbinger of encapsulating peritoneal sclerosis, but many cases of this condition show high rather than low transport characteristics in the early stages.[135]

Type III UFF is where lymphatic reabsorption of fluid from the peritoneal cavity is large enough to impair ultrafiltration. Peritoneal fluid absorption from the cavity occurs by two routes.[136] One is direct lymphatic absorption, occurring predominantly through diaphragmatic stomata. The other is hydrostatic pressure driven absorption of fluid across the peritoneal membrane into, predominantly, the tissues of the anterior abdominal wall. From here, the fluid is gradually resorbed, either by the lymphatics or directly into the systemic capillaries. The total fluid absorption by the two routes is difficult to measure but is thought to approximate 1 to 2 ml/min or 60 to 120 ml/hr. The main variation is thought to be in the direct lymphatic flow component. If this is significantly above the normal range, it is likely to become a clinical problem, especially if salt and water intake is high or urine volume is minimal. The proportion of cases of UFF due to this cause is unclear, but, in one review, Heimburger and colleagues[134] found that two of nine cases had high fluid resorption as the principal abnormality. In other cases, however, it may be a contributory factor.[127] In general, it is a diagnosis of exclusion because most PD units do not routinely measure peritoneal lymphatic flow or fluid absorption. Work by Fussholler and colleagues[137] suggests that peritoneal lymphatic flow does increase somewhat with time on PD.

Less common causes of UFF include aquaporin dysfunction and impaired hydraulic conductance of water by membrane.[136,138,139] The diagnosis of these is discussed in more detail in the chapter on PD physiology. In practice, these

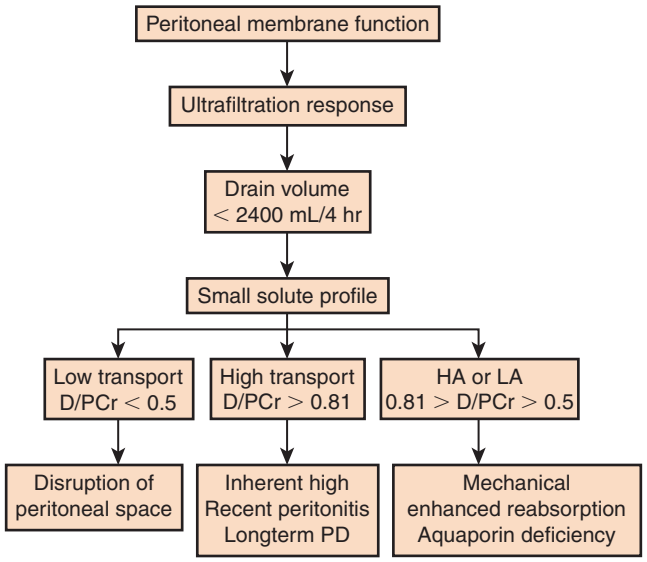


FIGURE 29-5 Management of fluid overload. (From S. Mujais, K. Nolph, R. Gokal, et al., Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis, Perit. Dial. Int. 20 [Suppl. 4] [2000] S43-S55.)

conditions will be suspected only when UFF occurs in the presence of relatively well-maintained peritoneal transport, and even then it is not easy to differentiate them from type III UFF. One clue to aquaporin dysfunction is a loss of the normal sodium sieving that occurs when hypertonic PD solutions are used.[127] However, this finding is not truly specific for aquaporin-related problems.

Investigation of fluid overload and UFF should follow the broad sequence outlined in the algorithms from the 1999 ISPD recommendations (Figure 29-5).[125] These emphasize history taking, clinical examination, inspection of dialysis records, and observation of catheter drainage. If a diagnosis is not then apparent, a PET using 4.25% dextrose is indicated and will allow a formal diagnosis of UFF to be made. The equilibration characteristics shown in the PET will then allow the UFF to be divided into the three distinct categories. Of course, many cases are multifactorial with, for example, a mixture of a membrane and a mechanical problem or perhaps a combination of excess lymphatic drainage issue and high salt intake.

IS AMBULATORY PERITONEAL DIALYSIS ASSOCIATED WITH LESS EFFECTIVE SALT REMOVAL?

Over the past decade, concerns have been expressed that the short duration cycles used in APD may predispose to poor salt removal relative to the long dwells of CAPD.[140,141] The theory is that short dwells maximize the effect of sodium sieving because the diffusive removal of sodium does not have time to occur.[32] Thus the ultrafiltrate during short cycles has a relatively lower concentration of sodium. A number of studies have suggested that this phenomenon is real with suggestions of higher rates of hypertension in APD patients.[140,141] However, these studies are not randomized trials, and an increasing literature comparing outcomes on CAPD with those on APD

has not demonstrated more volume-related problems or worse outcomes for those on APD.[142–144] The theoretical effects of sodium sieving on sodium removal in APD can be offset somewhat by use of a daytime icodextrin dwell.[141]

MANAGEMENT OF FLUID OVERLOAD

Management of fluid overload includes general and specific measures.[125] The general approach applicable to all cases is to review salt and water intake and to ensure that the patient is making appropriate choices of dialysate tonicity and is avoiding excessively long duration dwells, such as which may occur with the nocturnal dwell of CAPD or the daytime dwell of APD. Traditionally, PD patients have been allowed to liberalize salt intake, but in recent times, this has been questioned, and restriction is now commonly practiced and is certainly indicated in patients with volume overload or hypertension. In practice, sodium intake is often quite low in PD patients.[144]

An additional aspect of the general approach is to maximize urinary output using loop diuretics and ACE inhibitors or angiotensin receptor blockers.[59,60] Recent randomized, controlled trials are helpful in this regard. Medcalf and colleagues[61] have shown in a small placebo-controlled trial that furosemide 250 mg/day is associated with better preservation of urinary volume. Similarly, Li and colleagues[59] have shown in a randomized, controlled open-label study that ramipril 5 mg daily is associated with better preservation of renal clearance and with a lower probability of progression to anuria. These medications can easily be prescribed and are generally safe in the PD population, although the risk of volume depletion and disorders of serum potassium must be kept in mind.

More specific management measures depend on the cause of the fluid overload. Mechanical problems, such as leaks, hernias, and malfunctioning catheters will need surgical interventions. Noncompliance with the prescription, excess salt, and water intake, or inappropriate choice of solution tonicity requires educational interventions. Glycemic control may need attention.

In the case of type I UFF, long duration dwells are a particular problem. The simplest way to deal with this is to use the polyglucose solution, icodextrin, for the long dwell.[30] Icodextrin does not diffuse across the peritoneal membrane and so remains an effective osmotic agent, inducing ultrafiltration for many hours. Use of icodextrin is limited only by cost and by concerns that more than one dwell per 24-hour period might lead to accumulation of metabolites with unknown consequences. Wilkie and colleagues[145] have shown that icodextrin can prolong technique survival significantly in patients with UFF. Data from this study have been used to show that icodextrin, despite its expense, is a cost-effective intervention.[146] Two randomized controlled trials, in CAPD and APD, respectively, have confirmed that icodextrin, compared to glucose, is effective in reducing total body water, extracellular fluid volume, and echocardiographic measures such as left ventricular mass.[147,148] The main use of icodextrin for long dwells was initially in this setting of type I UFF. However, over the past decade, it has been increasingly used in patients without UFF, partly to avoid the problem and partly to avoid hypertonic glucose.

If icodextrin is unavailable for patients with Type I UFF, the long dwell can be shortened. In CAPD, this can be done by doing a drain in the middle of the night or, alternatively, a cycler based APD prescription can be introduced. The long day dwell in APD can be avoided by doing an extra exchange, either manually or from the cycler, midway through the day, or by simply draining the daytime fluid after 3 to 6 hours and leaving the patient "dry" until cycling commences again.[37]

In type II UFF, general measures may be tried, but PD is rarely viable because clearance and ultrafiltration are both compromised.

General measures are also the focus in management of type III UFF. Specific agents to decrease peritoneal lymphatic flow, such as lecithin, have been proposed but evidence to support their use has not been convincing.[149] Patients with type III UFF can also be maintained on PD because the problem is frequently moderate in severity and not progressive.

GLUCOSE-SPARING STRATEGIES

The concept of glucose-sparing strategies has become popular in recent time for two main reasons. First, the evidence that hypertonic glucose exposure is damaging to the peritoneal membrane has become stronger.[48,130,131] Second, and perhaps more significantly, there is a concern that systemic absorption of glucose from the dialysate has an adverse effect on the cardiovascular risk profile in that it may promote hyperglycemia, hyperlipidemia, hyperinsulinemia, and obesity. This latter concern has been heightened because of U.S. registry studies showing that patients with diabetes and with cardiovascular disease may do less well on PD, relative to HD, as compared to patients without these comorbid conditions.[150]

Glucose-sparing strategies can be divided into peritoneal and non peritoneal approaches. Non peritoneal approaches include salt and water restriction and the use of loop diuretics, ACE inhibitors, and angiotensin receptor blockers to maintain or increase urine output and so decrease the requirement for hypertonic glucose to maintain volume control. In general, aggressive volume depletion should be avoided. Peritoneal approaches include the use of alternative nonglucose solutions, such as icodextrin and amino acids. Often, these solutions are prescribed, not so much for their ultrafiltration or nutritional indications but rather because they are not glucose. More innovative peritoneal glucose sparing strategies that have been reported in recent times include cycling with glucose, icodextrin and amino acids mixes, mixed glucose icodextrin long dwells, and use of more than one icodextrin dwell daily.[118,151–154]

Glucose-sparing strategies are very attractive, and, although the evidence to justify them is circumstantial rather than conclusive, it seems prudent to follow them as far as is feasible. However, they should not be considered as a justification to leave volume overload and hypertension inadequately treated. The adverse effects of hypertension and fluid overload are likely more immediate than those of excess glucose exposure. However, a general approach of optimizing volume status while avoiding excess glucose exposure would be ideal.

CONCLUSION

An approach to optimizing PD adequacy involves prescribing the modality with attention to clearances, maintenance of good nutrition, and achievement of normal volume status. Such an integrated strategy is more likely to be successful than was the previous paradigm, which was largely limited to small solute clearance. Such an approach may also be helpful in improving the cardiovascular risk profile of these vulnerable patients.

A full list of references are available at www.expertconsult.com.

Chapter 30

PERITONEAL DIALYSIS-RELATED INFECTIONS

Szeto Cheuk-Chun, M.D., F.R.C.P. and
Philip Kam-Tao Li, M.D., F.R.C.P, F.A.C.P.

Peritoneal dialysis (PD) related infections are serious complications in PD patients.[1–3] Complications resulting from peritonitis and catheter infections include catheter loss;[4,5] transfer to hemodialysis, either permanent or temporary; hospitalization; and death.[6,7] Peritonitis is probably the most important cause of technique failure in PD patients.[2,3] In Hong Kong, over 16% of the deaths in patients being treated with PD are secondary to peritonitis.[8] Similarly, 18% of the infection-related mortality in PD patients results from perritonitis in the United States.[9]

During the early phase of the development of PD, peritonitis was common. For example, Rubin and colleagues[10] reported a rate of one episode per 1.9 patient-months at risk. The incidence of peritonitis decreased markedly over the following decade, largely as a result of improvements in connection technology.[11,12] More recently reported peritonitis rates are lower than one episode per 20 patient-months at risk.[13–15] However, there has been little reduction in the peritonitis rates over the past 10 years, and PD-related infection remains a major problem in dialysis practice.

PD infections result in technique failure, hospitalization, pain, and inconvenience to the patient. Less often, the consequence is death or peritoneal fibrosis. An understanding of the pathogenesis and management of PD is essential for the healthcare worker caring for these patients. Prevention of infection is critical to the success of a PD program.

PERITONITIS

Pathogenesis

PD-related peritonitis could be caused by touch contamination, catheter-related problems, bowel pathology, gynecological disease, or systemic bacteremia. The common microbiological causes of PD-related peritonitis are summarized in Table 30-1. Despite the advances in PD system connectology, contamination at the time of the PD exchange remains a major cause of peritonitis.[4,16] The following exchange practices are associated with peritonitis:[17,18]

- Touching the connection
- Dropping the tubing on the floor or table
- Not wearing a mask during the exchange
- Performing the exchange in an atmosphere filled with dust or animal hair

Holes in the catheter or tubing and accidental disconnections are obvious but uncommon causes of PD-related peritonitis.[19]

Organisms that are commonly grown from specimens in contamination-related peritonitis are coagulase-negative staphylococci (CNS) and diphtheroids (*Corynebacterium*).[15,18,20] Nasal carriers of *S. aureus* often have *S. aureus* on their hands and at the exit sites, which can lead to peritonitis through either touch contamination during connections or catheter-related

TABLE 30-1 Microbiological Causes of Peritonitis

Bacteria	80%-90%
▪ *S. epidermidis*	30%-45%
▪ *S. aureus*	10%-20%
▪ *Streptococcus* species	5%-10%
▪ *E. coli*	5%-10%
▪ Other gram negative species	5%
▪ *Pseudomonas* species	5%
▪ Others	<5%
▪ Mycobacterium	<1%
Fungus	<1%-10%
Culture negative	5%-20%

infection. Careful hand washing with a disinfectant followed by thorough drying of the hands is critical in reducing the risk of infection.[18] In addition, organisms found in the oral cavity, such as streptococci, may cause peritonitis if a mask is not worn during an exchange or may occur through transient bacteremia (for example, after a dental procedure).

Approximately 15% to 20% of peritonitis episodes are caused by catheter infection,[4,21] especially those resulting from *S. aureus* or *P. aeruginosa*. Exit-site infections can spread to involve the catheter tunnel and then the peritoneum.[21,22] Such infections are often refractory or relapsing.[28] In addition, there is substantial seasonal variation in the incidence of dialysis-related peritonitis, with peak incidence in the months that are hot and humid.[23,24] A warm and humid climate favors the accumulation of sweat and dirt around catheter exit site, and therefore the growth and colonization of bacteria.

Peritonitis, particularly in patients with multiple episodes of infection, is not uncommonly caused by the release of planktonic bacteria from biofilm on the walls of catheters.[25] In fact, bacteria can form biofilm on the walls of catheters within 48 hours of their placement. These bacteria within the slime layer are resistant to both host defenses and many antibiotics[26] and may be the cause of recurrent peritonitis.[27,28] This hypothesis is supported by the observation that catheter exchange after dialysis effluent clears up is effective in preventing the relapse of peritonitis.[29,30] However, biofilm is present in most patients undergoing PD after the catheter is in place for a time and in many cases do not result in peritonitis.[31] Peritoneal immune defenses are important in preventing peritonitis related to biofilm (see later discussion).[32]

Gram-negative bacteria that cause PD-related peritonitis, especially in the absence of known contamination or a catheter infection, are generally considered to originate from the bowel.[20] Similar to the spontaneous bacterial peritonitis in patients with liver cirrhosis, most of the cases of gram-negative PD-related peritonitis are due to transmural movement of bacteria rather than perforation.[33,34] Uremia per se is associated with impaired intestinal barrier function to macromolecules and possibly bacteria.[35] Constipation,[36] diarrhea,[37,38] and diverticular disease may predispose to such an event. Gastric acid inhibitors may also predispose to gram-negative peritonitis.[39] Intraabdominal disease, such as appendicitis, cholecystitis, or ischemic colitis, may also result in enteric peritonitis.[40,41]

Traditionally, polymicrobial peritonitis is believed to be caused by the perforation of internal viscera, and surgical exploration is often recommended.[42,43] Although previous guideline for the management of dialysis-related peritonitis by the International Society of Peritoneal Dialysis recommended early consideration of surgical exploration for polymicrobial peritonitis,[44] the recommendation was based on reports early after the invention of peritoneal dialysis.[42,43] Recent reports show that most of the patients with dialysis-related polymicrobial peritonitis responded to antibiotic therapy.[45,46]

Peritonitis may follow colonoscopy with polypectomy,[41] hysteroscopy,[47] endoscopy with sclerotherapy,[48] and dental procedures.[49] Peritonitis following dental procedures is most likely related to transient bacteremia. Vaginal leak of dialysate,[50] the use of intrauterine devices,[51] and endometrial biopsy[52] are other recognized causes of peritonitis. Because of the risk of peritonitis related to such procedures, antibiotic prophylaxis administered before any such procedure is necessary.

Host Defense Mechanisms of the Peritoneal Cavity

Uremia per se causes a wide spectrum of defects in the immunological defense against infection, which is beyond the scope of this chapter. Both humoral and cellular factors participate in the local peritoneal defense processes against peritonitis.[53] Theoretically, bacteria entering the peritoneal cavity are digested by peritoneal macrophages and neutrophils. Individual variation in the phagocyte function may partly account for interindividual differences in the incidence of peritonitis.[54] Here we will discuss only the relationship between abnormalities in peritoneal defense mechanisms and the frequency of peritonitis and the effect of dialysate on peritoneal defense mechanisms.[54–56]

Humoral Immunity

Opsonization of bacteria takes place when immunoglobulin G (IgG) molecules bind to specific epitopes on bacterial surface antigens through the antigen-binding site of the IgG molecule. In addition, microbial cell surface activates the complement system either directly through interaction with microbial polysaccharides through the alternate pathway, or indirectly through interaction with IgG or IgM bound to bacteria through the classic pathway. In vivo, both IgG and C3b are important opsonins. Phagocytic cells, either neutrophil or macrophage, have specific surface receptors for the Fc region of the IgG molecule and C3b. The opsonized microbe is ingested through receptor-mediated phagocytosis.[56] Phagocytosis is further amplified by fibronectin, which has binding sites for both macrophages and bacteria.

The concentrations of IgG, complement, and fibronectin in normal peritoneal fluid are similar to those in the normal serum. In peritoneal dialysis effluent, however, these values are reduced by 100- to 1000-fold,[57,58] even after several hours of dwell time. This dilutional effect severely compromises the humoral immunity within the peritoneal cavity. In patients receiving continuous ambulatory peritoneal dialysis (CAPD), an inverse

relationship between either peritoneal opsonic activity or IgG concentration and frequency of CAPD peritonitis has been reported.[32] However, peritoneal IgG levels failed to prospectively predict the risk for peritonitis[59] and IgG levels in spent dialysate vary markedly over time in any given patient.[59]

The opsonic activity of spent dialysate against gram-negative bacteria is substantially lower than that against gram-positive bacteria.[32] In fact, both IgG and C3b have different affinities for gram-negative and gram-positive organisms. This may account, at least in part, for the greater severity of the gram-negative peritonitis. Fibronectin has opsonic activity against gram-positive organisms,[56] especially *S. aureus*, but apparently not against gram-negative bacteria. Low concentrations of fibronectin in the spent dialysate have been found to be a risk factor of PD-related peritonitis.[57]

Cellular Immunity

The leukocyte count in peritoneal dialysis effluent is 100- to 1000-fold less than in normal peritoneal fluid.[55] The differential leukocyte counts in uninfected spent dialysate vary greatly among patients but remain stable over time in a given individual.[60] In general, macrophages predominate in spent dialysate; lymphocyte percentages may vary between 2% and 84%, and neutrophils are usually 5% to 10%.[60] However, baseline peritoneal leukocyte count is not associated with the risk of PD peritonitis.[60]

Mesothelial cells lining the serosal surface of the peritoneal membrane represent another important cell line in the defense against peritonitis and containment of infection within the peritoneal cavity.[61] The vital interaction between mesothelial cells and peritoneal macrophages early in the course of peritonitis occurs through cell-cell interaction and secretion of various inflammatory mediators.[61]

Resident peritoneal macrophages, believed to originate from blood monocytes, constitute the first line of defense against bacterial invasion of the peritoneal cavity. In the early stages of peritonitis, polymorphonuclear cells and macrophage migrate intraperitoneally from the systemic circulation and the interstitial matrix of the peritoneal membrane. Compared to cells from normal individuals, blood neutrophils from PD patients exhibit decreased binding of C5a, decreased chemotaxis, and impaired opsonic activity.[55]

In PD patients, phagocytic capacity of peritoneal macrophages incubated in culture media (i.e., not dialysis effluent) is normal.[53] Bacterial killing capacity of peritoneal macrophages studied in dialysate free media has been reported as either normal[53] or slightly decreased.[62] However, the oxidative metabolism of macrophages from noninfected spent dialysate is lower than that of macrophages from normal peritoneal fluid,[55] but higher than that of peripheral blood monocytes.[62]

The oxidative metabolism of peritoneal macrophages is impaired in PD patients with frequent peritonitis.[58] Moreover, peritoneal macrophages, in comparison to blood monocytes, exhibit increased binding capacity of C5a (a chemotactic factor) and expression of Fc receptors, HLA-DR (Ia) antigens and CD14 antigens (which binds bacterial lipopolysaccharide). Taken together, these findings suggest that peritoneal macrophages are activated in PD patients. Similar to peritoneal macrophage, T lymphocytes in peritoneal cavity, both helper and suppressor, appear to be activated in PD patients.[58] Recent evidence suggests that CD8 cytotoxic T lymphocytes may play a destructive role for the peritoneal membrane modified by advanced glycation end products.[63]

Effects of PD Solutions on Peritoneal Defense

The effects of PD solutions on peritoneal defense mechanisms are related to the dilution, high osmolality, low pH, lactate, and heat sterilization of the dialysate. In addition to the dilutional effects on humoral defense mechanisms, decreased density of peritoneal macrophages reduces the phagocyte-bacterium encounter and thus bacterial killing.[55] Both sustained high dialysate osmolality and low dialysate pH suppress peritoneal neutrophil and macrophage functions.[64] Although dialysate pH rises rapidly after intraperitoneal infusion and reaches blood pH by 30 minutes, the dialysate infusion period carries a high risk of bacterial entry at the same time that peritoneal defenses are compromised by low dialysate pH.

Lactate in commercial dialysate preparations appears to have independent adverse effects on peritoneal inflammatory cell function, specifically affecting macrophages, polymorphonuclear cells, mesothelial cells, and fibroblasts.[65] The development of peritoneal dialysis solutions containing nonlactate buffers may augment peritoneal defense mechanisms. The cytotoxicity of bicarbonate-based dialysate appears to be less than that of lactate-based dialysate. Some studies showed that bicarbonate-buffered dialysate might reduce the peritonitis risk, as compared to conventional lactate-based solution.[66] However, polymorphonuclear cell function studied in vitro after incubation in bicarbonate-based dialysate remains deficient.[67]

Presentation

Patients with peritonitis usually present with cloudy dialysis effluent and abdominal pain.[10] The severity of illness varies widely, depending on the etiological microorganism.[68] For example, *S. epidermidis* or diphtheroids often cause minimal abdominal pain. On the other hand, virulent organisms such as *S. aureus*, Pseudomonas aeruginosa, and fungi often cause severe abdominal pain and, not uncommonly, diarrhea. In general, fever indicates systemic sepsis. Hypotension indicates severe peritonitis.[68,69]

Diagnosis

Although most practicing nephrologists can diagnose PD-related peritonitis on clinical ground, the diagnosis needs to be confirmed by an effluent white blood cell (WBC) count, which should exceed 100 cells/μL (i.e., 0.1×10^9 cells per L), with more than 50% neutrophil. In the absence of peritonitis, the effluent WBC count is less than 25 cells/μL with primarily mononuclear cells.[70,71] If the patient is already taking antibiotics, a WBC count of 50 cells/μL or greater is suggestive of peritonitis. If the specimen is obtained after a short dwell time or in the absence of a dwell, the percentage of neutrophil (>50%) is a more sensitive marker than total WBC count.[72]

Occasionally, patients with peritonitis present with abdominal pain without cloudy effluent.[70,73] Koopmans and colleagues[73] reported that in 6% of peritonitis episodes, the effluent WBC count is initially less than 100 cells/μL. The effluent becomes

cloudy in most cases within a few hours. It is possible that patients who present with pain and the absence of cloudy effluent have delayed intraperitoneal cytokine response to the infection, signifying an underlying immunological abnormality.[73]

The differential diagnosis for infectious peritonitis includes chemical peritonitis, peritoneal eosinophilia, hemoperitoneum, pancreatitis, chylous effluent, and malignancy.[74] In peritoneal eosinophilia, a large number of eosinophil is present in the effluent. It usually occurs early in the course of PD, resolves spontaneously, and is usually not associated with infection.[75] The mechanism is generally believed to be allergic reaction to the plasticizers on the dialysis tubing, and the eosinophilia generally resolves spontaneously within 2 to 6 weeks.

Intraperitoneal administration of generic vancomycin[76] and amphotericin[77] can cause chemical peritonitis, which mimics bacterial infection. Sterile chemical peritonitis has also been reported following icodextrin treatment.[78] The episodes are characterized by mild abdominal discomfort, cloudy effluent with icodextrin dialysate only, dialysate leukocytosis with a predominance of macrophages and sterile cultures, and the absence of systemic symptoms.

A patient receiving PD who has pancreatitis may present with abdominal pain and cloudy peritoneal fluid, but cultures of the fluid are sterile and the effluent amylase concentration should be greater than 100 Units/L.[79] Chylous ascites is a rare cause of sterile cloudy effluent, and the effluent WBC count is normal.[80] Patients with intraabdominal malignancy may also have cloudy effluent, and the diagnosis can be established by cytological evaluation.[81]

TREATMENT OF PERITONITIS

Initial Evaluation

In patient presenting with possible peritonitis, evaluation should include close questioning about a history of possible touch contamination, compliance in sterile dialysis technique, recent procedures that may have led to peritonitis, and change in bowel habits, either diarrhea or constipation. The physician should review any history of peritonitis to assess for the possibility of recurrent peritonitis with the same organism or previous infection with a methicillin-resistant organism. In addition to the usual physical examination, one must carefully assess the exit site and tunnel for edema, erythema, tenderness, and discharge. The effluent should be examined, and specimens should be collected for cell count, differential count, Gram stain, and culture. The Gram stain result, if positive, is helpful in guiding the choice of antibiotic therapy.[82] Rapid institution of treatment once the appropriate assessment is completed is essential.

Despite a careful history, physical examination, and Gram stain of the effluent, empirical treatment of peritonitis frequently has to be initiated in the absence of appropriate diagnostic information. An arbitrary decision regarding antibiotic therapy must be made after considering the likely causative organisms.[44,83] A few novel diagnostic techniques, including leukocyte esterase reagent strip, broad-spectrum polymerase chain reaction (PCR) with RNA sequencing, quantitative bacterial DNA PCR assays, and matrix metalloproteinase-9 (MMP-9) test kit may hold the promise of providing an early and reliable diagnosis,[84,85] but these strategies require further evaluation.

Evolving Trend of Empirical Therapy

There is a growing consensus for a standardized approach, which combines the continuation of peritoneal dialysis with intraperitoneal administration of antibiotics. Such an approach has been further emphasized in the 2000 and 2005 updates of the Advisory Committee on Peritoneal Dialysis (a subcommittee of the ISPD).[44,74]

In their 1993 recommendations, this Ad Hoc Committee advocated 1) the use of vancomycin to treat gram-positive infections, 2) the use of ceftazidime or aminoglycoside to cover the gram-negative organisms as first-line agents, and 3) empirical therapy if an organism has not been identified on Gram stain at presentation.[83] Since the publication of that report, however, increasing numbers of vancomycin-resistant microorganisms have emerged, a trend that has been particularly evident in larger hospitals. As a result, the use of vancomycin is discouraged for prophylaxis, for routine use, and for use in oral form against *Clostridium difficile* enterocolitis.[86,87] The major concern is that the vancomycin resistance will be transmitted to staphylococcal strains, creating a situation of major epidemiological importance. In fact, a case of vancomycin-resistant, CNS peritonitis in a patient being treated with PD has been reported.[88] This situation has prompted the Ad Hoc Committee to move away from the use of vancomycin as a first-line therapy, and in 1996 the ISPD subcommittee on peritonitis has reverted to recommending use of first-generation cephalosporins in large doses for all cases.[89] Based on published literature, there is no significant difference in clinical response or relapse rate between vancomycin and cefazolin as the initial antibiotic for gram-positive peritonitis.[90] Furthermore, empirical treatment with intraperitoneal cefazolin was as effective as vancomycin for *S. epidermidis* peritonitis despite a high prevalence of methicillin resistance.[91]

Many authorities, however, continue to advocate vancomycin as the first-line therapy in spite of the concern on Vancomycin-resistant enterococcus (VRE). For example, Sandoe and colleagues[92] found that at least 50% of cases of peritonitis due to CNS would not be adequately treated with a cephalosporin. The reasons given for continuing to use vancomycin were the low prevalence of VRE and a high prevalence for CNS methicillin resistance. In short, each program should assess the local patterns of sensitivity and methicillin resistance before a decision is made whether to use vancomycin or cephalosporin for initial therapy of peritonitis. This center-based approach was again emphasized in the most recent Ad Hoc Committee Recommendations in 2005.[74]

In their 1996 recommendations, the Ad Hoc Committee Recommendations involved the use of a combination of a first-generation cephalosporin and an aminoglycoside.[89] However, there is some evidence suggesting a more rapid loss of residual renal function in patients receiving aminoglycosides.[93] Because residual renal function is an independent predictor of patient survival,[94] there has been a growing concern to avoid routine use of aminoglycoside so as to preserve residual renal function. As a result, in their 2000 recommendations, the Ad Hoc Committee recommended ceftazidime,

instead of an aminoglycoside, as empirical therapy for coverage of gram-negative organisms in patients with significant residual renal function,[44] which was arbitrarily defined as a daily urine output of 100 ml or more. In a subsequent randomized control study of 102 patients, however, intraperitoneal cefazolin plus netilmicin and cefazolin plus ceftazidime have similar efficacy as empirical treatment for PD peritonitis and a similar effect on residual renal function.[95] In the latest Ad Hoc Committee Recommendations in 2005,[74] either gentamicin or ceftazidime is an acceptable choice for the initial empirical coverage of gram-negative organisms. Although empirical monotherapy of broad-spectrum antibiotic is an attractive alternative, and certain success has been reported from the use of cefepime[96] and imipenem-cilastatin,[97] the evidence is preliminary, and empirical combination antibiotics remains the standard of practice.

Figure 30-1 is an algorithm for the assessment and antibiotic therapy of peritonitis. In the latest Ad Hoc Committee Recommendations,[74] gram-positive organisms may be covered by vancomycin or a cephalosporin, and gram-negative organisms by a third-generation cephalosporin or aminoglycoside. Table 30-2 lists the suitable agents and dosages. The rationale for using the recommended large dose of a first-generation cephalosporin is that the organisms are in fact "sensitive" to the drug because of the high local level achieved at the site of the infection (i.e., within the peritoneal cavity).

TABLE 30-2 Empirical Initial Therapy for Peritoneal Dialysis-Related Peritonitis

(A) Gram-positive coverage
▪ Cefazolin
- Intermittent: 15 mg/kg daily
- Continuous: 500 mg/L loading, 125 mg/L maintenance
- APD: 20 mg/kg daily in long day dwell
▪ Vancomycin
- Intermittent: 15-30 mg/kg every 5-7 days
- Continuous: 1000 mg/L loading, 25 mg/L maintenance
- APD: 30 mg/kg loading in long dwell, repeat dosing 15 mg/kg in long dwell every 3-5 days, following levels
(B) Gram-negative coverage
▪ Ceftazidime
- Intermittent: 1000-1500 mg daily
- Continuous: 500 mg/L loading, 125 mg/L maintenance
- APD: cefepime 1 g in one exchange daily
▪ Aminoglycoside (gentamicin/netilmicin/tobramycin)
- intermittent: 0.6 mg/kg daily
- Continuous: 8 mg/L loading, 4 mg/L maintenance
- APD: 1.5 mg/kg loading in long dwell, then 0.5 mg/kg daily in long dwell
NB. In patients with residual renal function (defined as >100 ml/day urine output), dose should be empirically increased by 25%.

APD, automated peritoneal dialysis.

Once-Daily Antibiotic Therapy

A controversial area is the use of once-daily antibiotic therapy, which has the obvious advantage of ease of use by patient and staff. More importantly, there are theoretical advantages to administering aminoglycosides as a single dose in a long-dwell exchange.[98] Aminoglycosides given as a single daily dose may result in less ototoxicity and nephrotoxicity[98] and improved bacterial killing in association with prolonged post antibiotic effect. In a pharmacokinetic study by Low and colleagues,[99] intraperitoneal (IP) gentamicin 0.6 mg/kg was given in one exchange with a 6-hour dwell. Intraperitoneal drug levels were high throughout the dwell, but negligible thereafter. Serum levels remained low.

Lai and colleagues[98] studied the efficacy of once-daily IP cefazolin and gentamicin for treatment of peritonitis. Of the 14 episodes of gram-negative peritonitis in the series, six were due to *Pseudomonas* and required alteration in therapy. In spite of the change in therapy, catheter removal was eventually needed in three of the cases. One third of the non-*Pseudomonas* gram-negative infections required alteration of therapy. Bailie and colleagues[100] used once daily gentamicin (in combination with an initial dose of vancomycin) and reported resolution of two thirds of the non-*Pseudomonas* gram-negative peritonitis episodes in their patients. The "nonresponder" organisms include *Acinetobacter* and *Alcaligenes* species. These results show that gentamicin given in one exchange per day provides adequate coverage for gram-negative organisms for most of the peritonitis episodes.

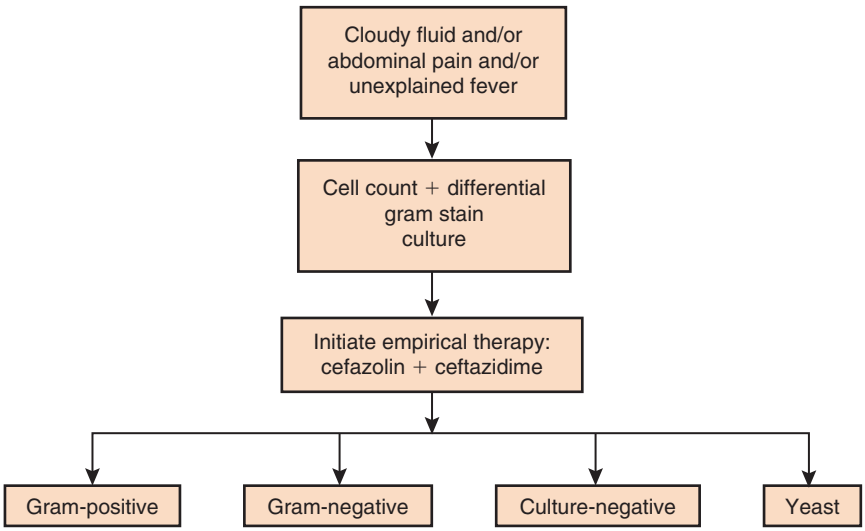


FIGURE 30-1 Algorithm of the initial assessment and therapy for peritoneal dialysis infections.

There is, however, incomplete evidence for this practice. In the study of once-daily IP cefazolin and gentamicin by Lai and colleagues,[98] all 19 episodes of gram-positive peritonitis resolved, with only one infection resulting from *S. aureus*, requiring modification of the initial therapy. The organisms in three episodes of *S. epidermidis* in this study were shown by sensitivity testing to be resistant to both gentamicin and cefazolin yet responded to therapy with these agents. In another study reported by Goldberg and colleagues,[101] once-daily IP cefazolin for the initial treatment of PD-related peritonitis was at least as effective as the historical control of a vancomycin-based regimen. However, it is important to note that episodes of peritonitis with associated catheter infection were excluded from both of the studies, accounting in part for the excellent results. A recent systematic review of available literature concluded that IP administration of antibiotics is superior to IV dosing for treating PD peritonitis, and intermittent and continuous dosing of antibiotics are equally efficacious.[102]

Other Considerations of Drug Delivery

In a retrospective study of 613 patients, Blunden and colleagues[103] confirmed that dosing guideline for vancomycin in CAPD and automated peritoneal dialysis (APD) patients produces adequate serum concentrations of the antibiotics in the vast majority. However, large incremental dosing of vancomycin is needed if day-5 levels are low, especially for nonanuric patients. In contrast, the currently recommended dosing regimen of gentamicin resulted in high levels for >50% patients, but switching gentamicin to ceftazidime at day 5 appeared safe and limited aminoglycoside exposure. In this study, increasing vancomycin and gentamicin concentrations do not appear to improve cure rates.[103] Because standard microbiological tests (e.g., MIC) do not account for the unique factors of PD peritonitis, it has been suggested that the peritoneal fluid inhibitory titers were better associated with clinical outcome.[104]

Therapy for Specific Organisms

Gram-Positive Microorganisms

The therapy for gram-positive peritonitis is outlined in Table 30-3. Peritonitis episodes caused by CNS, *S. aureus*, and *Streptococcus* are distinctly different in presentation, pathogenesis, and outcome. Therapy must therefore be individualized.

Coagulase-Negative Staphylococci For CNS, the first-generation cephalosporins are usually sufficient. If, however, the organism is methicillin-resistant *S. epidermidis* (MRSE), vancomycin or clindamycin should be used. Cefazolin tends to be less effective than vancomycin for the treatment of MRSE peritonitis. In a study by Vas and colleagues,[105] there was no difference in cure rates for the two agents in treatment of CNS that were methicillin-sensitive (92% for vancomycin versus 100% for cefazolin). For MRSE, however, the cure rate was 73% for vancomycin and only 45% for cefazolin. In a recent retrospective study of 232 cases of CNS peritonitis, methicillin resistance was common but the treatment outcome remains favorable when cefazolin is used as the empirical first-line antibiotic.[106]

Recurrent peritonitis must be treated aggressively. A 3-week course of antibiotic may achieve a higher cure rate in relapse or repeat episodes.[106] To prevent further relapse of peritonitis, the catheter may be replaced as a single procedure after the dialysis effluent clears up with antibiotics.[107] Alternatively, the use of fibrinolytic agents, such as urokinase (5000 unit in 5 ml normal saline injected into the catheter with the abdomen drained and allowed to dwell for 2 hours), is successful in approximately 50% of the patients with recurrent CNS peritonitis.[108] In a randomized study, Williams and colleagues[108] found that catheter replacement was superior to urokinase in preventing further relapse. Our own experience suggests that a higher dose of urokinase remains well-tolerated and is possibly more efficacious. Nonetheless, thrombolytic therapy should be reserved for infections for which no other cause or complication is evident (e.g., tunnel infection) and probably should be limited to CNS or culture-negative infection.

Staphylococcus aureus *S. aureus* is the major cause of exit site and tunnel infections and is also an important cause of peritonitis.[109] Patients with *S. aureus* peritonitis often have severe abdominal pain, require hospitalization, and may require catheter removal for resolution, especially when a concomitant tunnel infection is present.[68] *S. aureus* peritonitis occurs predominantly in patients who have a history of *S. aureus* catheter infections. Patients who have *S. aureus* colonization in the nares,[110,111] on the skin,[112] or at the peritoneal catheter exit site[112] are at particular risk of developing *S. aureus* peritonitis. Even one positive nose culture increases the risk of *S. aureus* peritonitis.[110,113]

TABLE 30-3 Treatment Strategies After Identification of Gram-Positive Organism on Culture

ENTEROCOCCUS	STAPHYLOCOCCUS AUREUS	OTHER GRAM-POSITIVE ORGANISM (COAGULASE-NEGATIVE STAPHYLOCOCCUS)
AT 24 TO 48 HOURS		
▪ Stop cephalosporins ▪ Start ampicillin 125 mg/L/bag ▪ Consider adding aminoglycoside ▪ If ampicillin-resistant, start vancomycin or clindamycin	▪ Stop ceftazidime or aminoglycoside, continue cefazolin ▪ Add rifampin 600 mg/day, oral ▪ If MRSA, start vancomycin or clindamycin	▪ Stop ceftazidime or aminoglyside, continue cefazolin ▪ If MRSE and clinically not responding, start vancomycin or clindamycin
DURATION OF THERAPY		
▪ 14 days	▪ 21 days	▪ 14 days
AT 96 HOURS		
▪ If no improvement, reculture and evaluation for exit-site or tunnel infection, catheter colonization, etc. ▪ Choice of final therapy should always be guided by antibiotic sensitivities.		

MRSA, methicillin-resistant *S. aureus*; *MRSE,* methicillin-resistant enterococcus; *VRE,* vancomycin-resistant enterococcus.
Data from W.F. Keane, G.R. Bailie, E. Boeschoten, et al., Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update, Perit. Dial. Int. 20 (2000) 396–411.

After empirical therapy and once the organism is identified as *S. aureus*, its sensitivity to methicillin will dictate further choice of antibiotics. If the organism is sensitive to methicillin, cefazolin should be continued. We prefer adding rifampin (600 mg/day) orally to the IP cephalosporin in all cases of *S. aureus* peritonitis. Vancomycin and cefazolin have similar efficacy in the treatment of methicillin-sensitive *S. aureus* peritonitis. For example, Vas and colleagues[101] reported that 58% of cases of *S. aureus* peritonitis resolved with vancomycin treatment, and 67% with cefazolin. In another review of 245 cases of *S. aureus* peritonitis, episodes that were treated initially with vancomycin had better primary response rate than those that were treated with cefazolin (98.0% versus 85.2%), but the complete cure rate was similar.[114] The cure rate for *S. aureus* peritonitis is relatively low because concomitant catheter infections are common. Adjuvant rifampicin treatment seems to associate with a significantly lower risk for relapse or repeat *S. aureus* peritonitis than was treatment without rifampicin (21.4% versus 42.8%).[114] Removal of the catheter should be considered early if a concomitant exit site or tunnel infection is present.

Recent hospitalization is a major risk factor of methicillin resistance.[114] If methicillin resistant *S. aureus* (MRSA) is isolated from dialysis effluent, rifampin should be added and the cephalosporins should be replaced by vancomycin. The vancomycin (up to 2 g IP, depending on body weight) may be repeated every 5 to 7 days. To avoid inadequate treatment, therapeutic drug monitoring and more frequent vancomycin dosage may be needed in selected cases with substantial residual renal function. Unfortunately, MRSA peritonitis is always difficult to treat and frequently requires catheter removal.[115]

Streptococci A respiratory, cutaneous, digestive or urinary tract infection precedes Streptococcal peritonitis episode in 25% of patients.[116] It is our experience that most cases of peritonitis caused by *Streptococci* have satisfactory response to 2-week course of IP cefazolin. Alternatively, 90% of cases respond to ampicillin, which appear to be more effective than vancomycin. Isolated infections with viridans streptococci seem to associate with slower response, poor outcome, and higher rates of recurrence.[117]

Enterococci In contrast to *S. viridans*, the occurrence of enterococcus peritonitis has not been decreased with the use of disconnect systems, probably because enterococcal infection is related more to a bowel source than to contamination or bacteremia.[116] As a rule, enterococcal infection does not respond to cephalosporins. Peritonitis caused by enterococcus is severe and has a slower response to antibiotics,[116] partly as a result of the current Ad Hoc Committee Recommendation of cephalosporins as initial therapy. Although still fairly uncommon in patients undergoing PD, VRE peritonitis has been reported by Troidle and colleagues.[117] VRE peritonitis is associated with previous hospitalization and antibiotic use (particularly cephalosporins and vancomycin) and has a high mortality rate even with catheter removal.

Gram-Negative Organisms

Peritonitis caused by gram-negative organisms is often associated with fever, nausea, vomiting, and abdominal pain. The care of gram-negative peritonitis is summarized in Table 30-4. Good results have been reported with either IP aminoglycoside or ceftazidime.[118] Alternatively, quinolones, which have the advantage of convenient oral administration, can be used with acceptable result.[119]

Pseudomonas and Stenotrophomonas Recent antibiotic therapy is the major risk factor of Pseudomonas peritonitis.[120] Patients with immunosuppression are also at higher risk for Pseudomonas peritonitis.[121] If the effluent culture reveals a *Pseudomonas* infection, especially one caused by *P. aeruginosa*, the ceftazidime should be continued, and a second antipseudomonal agent should be added to the regimen. In general, IP gentamicin or oral ciprofloxacin are reasonable choices. One needs to look carefully for evidence of catheter infection. Exit-site infection and recent antibiotic therapy are associated with poor therapeutic response to antibiotics.[120] When therapeutic response is suboptimal, early catheter removal may help preserving the peritoneum for further peritoneal dialysis. Elective catheter exchange after clear up of PDE may also reduce subsequent relapse.[120]

Stenotrophomonas maltophilia, a common environmental organism, is the cause of 1.5% of all peritonitis episodes.[122] Recent bacterial peritonitis with broad-spectrum antibiotics therapy was the major risk factor. The outcome was poor with medical treatment alone. Treatment should consist of two antibiotics, such as ceftazidime and cotrimoxazole. However, fungal peritonitis was a common consequence, probably related to the prolonged course of antibiotics.[122] Most, if not all, patients required removal of catheter eventually, either because of the effluent failed to clear up, or because of secondary peritonitis.

Other Gram-Negative Bacteria Single-organism, gram-negative peritonitis may be the result of touch contamination, exit-site infection, or transmural migration from constipation or colitis. A recent retrospective study of *Enterobacteriaceae* peritonitis showed that recent antibiotic therapy is the major

TABLE 30-4 Treatment Recommendations if a Gram-Negative Organism is Identified on Culture at 24 to 48 Hours

SINGLE GRAM-NEGATIVE ORGANISM	PSEUDOMONAS/STENOTROPHOMONAS	MULTIPLE GRAM-NEGATIVE AND/OR ANAEROBES
	AT 24 TO 48 HOURS	
▪ Stop cefazolin ▪ Continue ceftazidime or aminoglycoside ▪ Adjust antibiotics according to sensitivity	▪ Stop cefazolin, continue ceftazidime ▪ If urine <100 ml/day, add aminoglycoside ▪ If urine >100 ml/day, add ciprofloxacin 500 mg p.o. b.i.d. or piperacillin 4 gm IV q12 hours or sulfamethoxazole/trimethoprim 1-2 DS/day or aztreonam load 1 g/L; maintenance dose 250 mg/L IP/bag	▪ Continue cefazolin and ceftazidime ▪ Add metronidazole 500 mg q8 hours p.o., IV, or rectally ▪ If no change in clinical status, consider surgical intervention
	DURATION OF THERAPY	
▪ 14 days	▪ 21 days	▪ 14 days

DS, double strength; *IP,* intraperitoneally; *IV,* intravenously.
Data from W.F. Keane, G.R. Bailie, E. Boeschoten, et al., Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update, Perit. Dial. Int. 20 (2000) 396–411.

risk factor of antibiotic resistance; exit-site infection, and probably recent antibiotic therapy, is associated with poor therapeutic response.[123] There is also evidence that two antibiotics may reduce the risk of relapse and recurrence, as compared to single agent therapy.[123]

Enteric and Polymicrobial Peritonitis Polymicrobial peritonitis is a serious complication in peritoneal dialysis patients and is present in 6% to 11% of all peritonitis episodes.[45,46] Traditionally, perforation of internal viscous and underlying gastrointestinal pathology is believed to be the cause but many cases may be the result of touch contamination or catheter infection. Response to antibiotics is excellent when only gram-positive organisms are isolated from dialysis fluid, which accounts for approximately one third of the polymicrobial peritonitis episodes.[124] The presence of fungus, anaerobes, and *Pseudomonas* species in dialysis fluid are independent predictors of poor response to antibiotic therapy. Pooled analysis of four case series[45,46] shows that less than 6% of the polymicrobial peritonitis has a surgical cause. Although it is possible that some of the cases with underlying surgical pathology responded to conservative management and were not identified, the finding suggests that surgical pathology that needs aggressive surgical intervention is uncommon. Nonetheless, the clinical presentation with hypotension, sepsis, lactic acidosis, or elevation of peritoneal fluid amylase should raise immediate concern for "surgical" peritonitis and urgent intervention.[125]

Intraabdominal abscess is an uncommon complication of PD-related peritonitis, occurring in 0.7% of all peritonitis episodes. Abscess is more common following *P. aeruginosa*, *Candida albicans*, and polymicrobial peritonitis.[126] Persistent fever, abdominal tenderness and peripheral leukocytosis despite antibiotic therapy and catheter removal are all consistent with this diagnosis, which can then be confirmed by computed tomography scan or ultrasonography. The abscesses require drainage.

FUNGAL ORGANISMS

Fungal peritonitis occurs in patients undergoing PD at the rate of 0.01 to 0.19 episodes per dialysis-year, accounting for 3% to 6% of episodes.[7,127,128] Over 70% of the episodes of fungal peritonitis are caused by *Candida* species.[128,129] Recent antibiotic therapy, frequent episodes of bacterial peritonitis, and immunosuppression are the major risk factors of fungal peritonitis.[130] Patients are often severely ill with marked abdominal tenderness.[129,131]

Catheter removal is recommended immediately after fungi are identified.[74] Initial therapy may be a combination of amphotericin B and flucytosine until the culture results are available with susceptibilities. Caspofungin, fluconazole, or voriconazole may replace amphotericin B, based on species identification and MIC values. Intraperitoneal use of amphotericin is not advisable because of chemical peritonitis, but IV use has a poor peritoneal penetration. Voriconazole is an alternative for amphotericin B when filamentous fungi have been cultured and can be used alone for Candida peritonitis with catheter removal. If flucytosine is used, regular monitoring of serum concentrations is necessary to avoid bone marrow toxicity. Therapy should be continued after catheter removal, orally with flucytosine and fluconazole for an additional 10 days.[74]

MYCOBACTERIUM PERITONITIS

Tuberculous peritonitis is rarely seen in peritoneal dialysis patients in the Western world, but is more common in Asian countries. Contrary to the common belief, the WBCs in the effluent are predominantly polymorphonuclear cells, and an acid-fast bacilli stain of an effluent specimen is generally negative.[132] Abnormal chest radiograph findings and ascitic fluid lymphocytosis could only identify 33% and 37% of the cases, respectively.[133] Conventional microbiological diagnostic methods are slow and may not be sensitive enough for establishing a diagnosis in a timely manner. Standard antituberculous chemotherapy is highly effective,[132,133] although ultrafiltration failure may occur if PD is continued.[134] Advanced age and delayed initiation of therapy are associated with higher mortality rates.[133]

At least in subtropical countries, there seems a recent increase in incidence of peritonitis caused by atypical mycobacterium. Although the case remains controversial, it has been postulated that extensive use of topical gentamicin ointment for exit-site infection might predispose patients to atypical mycobacterial infection.[135]

CULTURE-NEGATIVE PERITONITIS

In approximately 14% to 20% of episodes that meet the criteria for peritonitis on the basis of cell count, culture of the effluent results in no growth of organisms. Most of the culture-negative peritonitis could be explained by recent antibiotic therapy or technical problems during dialysate culture.[136] Placing 5 ml of the effluent into trypticase soy broth-blood culture bottles (aerobic and anaerobic) decreases the rate of negative culture results to 25% compared with a 50-ml centrifugation culture technique, for which the rate is 42%. On the other hand, approximately 75% of patients presenting with peritonitis, when tested for the presence of antibiotics (some taken surreptitiously), have sterile cultures. In cases of no growth, repeated culture of the effluent results in identification of an organism in about one third of episodes.

In general, therapeutic decision should be reviewed after 24 to 48 hours of empirical antibiotic therapy. If the patient is improving clinically, the initial therapy can be continued, although aminoglycoside is generally not necessary.[74] Duration of therapy should be 2 weeks if the effluent clears rapidly. If, on the other hand, improvement is inadequate by 5 days, catheter removal should be strongly considered.[74]

Reassessment after 48 Hours of Therapy

Most patients with PD-related peritonitis show considerable clinical improvement within 2 days of starting antibiotics. Occasionally symptoms persist beyond 48 to 96 hours. At 96 hours, if a patient has not shown definitive clinical improvement, a reevaluation is essential. Dialysis effluent cell counts, Gram stain, and cultures should be repeated. Antibiotic removal techniques may be used in an attempt to maximize culture yield. A recent study showed that peritoneal dialysate white count $\geq 1090/mm^3$ on day 3 was an independent prognostic marker for treatment failure after adjustment for conventional risk factors.[137] Catheter removal should be considered if the response

TABLE 30-5 Terminology of Peritonitis[74]

Recurrent	An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
Relapsing	An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode
Repeat	An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
Refractory	Failure of the effluent to clear after 5 days of appropriate antibiotics

Data from B. Piraino, G.R. Bailie, J. Bernardini, et al., Peritoneal dialysis-related infections recommendations: 2005 update, Perit. Dial. Int. 25 (2005) 107–131.

to antibiotic therapy is poor after 96 hours. In a recent randomized control trial of 88 patients, intraperitoneal urokinase has no significant benefit as an adjunct therapy in the treatment of bacterial peritonitis resistant to initial antibiotic therapy.[138]

One should be aware of the presence of unusual organisms, such as mycobacteria, fungi, or fastidious organisms, which require specific cultures, and the potential of surgical disorders. If *S. aureus* and *P. aeruginosa* peritonitis are related to catheter or tunnel infection, catheter removal should be considered.

Special Considerations

Refractory and Relapsing Peritonitis

Current terminology of peritonitis is summarized in Table 30-5. Catheter removal should be considered in most cases of refractory peritonitis. Catheter exchange after dialysis effluent clears up is also effective in preventing the relapse of peritonitis.[29,30]

Peritonitis in Patients Undergoing Automated Peritoneal Dialysis As in CAPD peritonitis, the majority of APD peritonitis episodes are caused by gram-positive bacteria. In a randomized study comparing continuous cyclic PD (CCPD) with CAPD using a Y-connector, peritonitis rates were lower with the former (0.51 and 0.94 per dialysis year at risk, respectively).[139] Holley and colleagues,[140] using case controls, also found peritonitis rates to be lower in patients undergoing CCPD than in patients undergoing CAPD using Y-connectors (0.3 versus 0.5 per dialysis year at risk, respectively). Rates may be lower with CCPD because of longer dwell times, which result in improved peritoneal macrophage functioning and opsonic activity, thereby leading to better host defense.[141] Leaving the peritoneal cavity free of fluid during the day time (dry days), as in nocturnal intermittent PD, offers no further improvement in peritoneal macrophage functioning.[142]

The choice of first-line antibiotics in CAPD applies also to APD (see Table 30-3). In many centers, during peritonitis, APD patients are changed to a CAPD schedule because it is then easier to evaluate the clinical course using standardized procedures for obtaining dialysate for cell count and culture and sensitivity. Furthermore, the recommendations for antibiotic treatment are based mainly on data obtained using CAPD and limited experience in APD.[143] There is limited report on the clinical outcome of peritonitis in APD patients.[144] Attention should be given to an adequate dwell time of at least 4 hours to allow absorption of antibiotic agents. As with CAPD, adjustments for APD prescription may be needed in patients who experience altered ultrafiltration during episodes of peritonitis.

Peritoneal Lavage

As discussed previously, fresh dialysis solutions have detrimental effect on the local peritoneal defense mechanisms.[145] Rapid-exchange peritoneal lavage is therefore not advisable in the management of peritoneal infection. After two to three in-and-out exchanges that remove inflammatory products and lessen abdominal pain, CAPD should be resumed with usual long-dwell exchanges. Ejlersen and colleagues[146] reported poor outcome in patients treated with 24 hours of initial lavage. Peritoneal lavage, however, is still indicated before surgical exploration in cases of fecal peritonitis.

Nevertheless, ultrafiltration problem is common during acute peritonitis because peritoneal permeability is increased during an episode of peritonitis.[147] The dwell time may therefore have to be shortened or the dialysate dextrose level increased. The use of dialysate containing icodextrin in this situation has been shown to improve ultrafiltration.[148]

Catheter Removal

Infections are the cause of catheter removal in approximately 85% of cases.[4] *S. aureus* and *Pseudomonas* species are the common organisms responsible for the greatest catheter loss.[109,120] It is usually suggested that after an episode of severe peritonitis that requires catheter removal, peritoneal dialysis can be resumed after a minimum of three weeks. In a series of 100 CAPD patients with catheter removed for severe peritonitis, catheter was successfully reinserted, and peritoneal dialysis was resumed in 51 cases, and 45 of them required additional dialysis exchanges or hypertonic dialysate to compensate for the loss of solute clearance or ultrafiltration, although there was no significant change in dialysis adequacy or nutritional status.[149] Another recent review of 189 peritonitis episodes by Troidle and colleagues[150] found that only 47% of the patients underwent a successful catheter reinsertion; of those, only 34% remained on PD 1 year later.

On the other hand, if a catheter is removed for catheter infection or relapsing or recurrent peritonitis with clear effluent, it can be placed simultaneously.[107,151] It is critical that the effluent WBC count be less than 200 cells/L before one can proceed with simultaneous removal and replacement of a catheter.[152] Data suggest that this is a feasible procedure that decreases costs and minimizes the use of temporary hemodialysis. If the peritonitis can be transiently cleared in a patient with relapsing *Pseudomonas* peritonitis, simultaneous removal and replacement of the catheter may be feasible.[120,152] Simultaneous removal and reinsertion of catheters is also a safe and effective method for the treatment of refractory exit-site infection.[153] However, this approach is not advisable for fungal peritonitis.

Complications

Peritonitis results in a marked increase in effluent protein losses, which may contribute to the protein malnutrition of PD patients.[154] More importantly, ultrafiltration problem is common during acute peritonitis because peritoneal permeability is increased during an episode of peritonitis.[147] The pH of the effluent falls, especially in the presence of gram-negative peritonitis, and results in a further impairment of neutrophil activity.[155] These physiological changes in the peritoneal membrane are usually transient.[156] However, after an episode of

severe peritonitis, an increase in solute transport and loss of ultrafiltration may occur, resulting in a hyperpermeable membrane and permanent loss of ultrafiltration capability.[149,157] This process is probably proportional to the extent of inflammation and the number of peritonitis episodes.[158]

The final stage of this process is peritoneal fibrosis, sometimes referred to as sclerosing encapsulating peritonitis (SEP).[157] SEP is possibly more common in Japan, and the condition is present in 0.9% of patients undergoing PD.[159] The peritonitis rate among patients who experienced SEP was 3.3 times higher than that among the rest of the patients. Peritoneal fibrosis is a severe complication of PD. In addition to ultrafiltration failure, the patient becomes progressively malnourished because of recurrent partial intestinal obstruction from encasement of the bowel. PD cannot be continued and this complication is frequently lethal despite conversion to long-term hemodialysis.

CATHETER INFECTIONS

Colonization of the PD catheter exit site with bacteria may lead to infection of the catheter exit site, which may further spread along the subcutaneous tunnel of the catheter to the inner cuff and subsequently to the peritoneum, resulting in tunnel infection and peritonitis respectively. Catheter infection generally encompasses both exit-site and tunnel infections and occurs at an incidence of around one episode per 20 patient-months of treatment. However, reported figures varying considerably because definitions have not been standardized in the literature.[9] In general, *S. aureus* and *P. aeruginosa* are the most common and infection with either of these two organisms is difficult to resolve and commonly results in peritonitis and catheter loss.[21,35] However, the prevalence of individual organism varies markedly in different centers. Lye and colleagues[160] reported that 77% of all catheter infections is caused by *S. aureus* and 11% caused by *Pseudomonas* species. In our center in Hong Kong, 46% of all catheter infections is caused by Staphylococcal species, 28% caused by Pseudomonas species, and 13% caused by other gram-negative bacteria (our unpublished data).

Definitions

PD catheter infection includes exit-site infection and tunnel infection. The classification of catheter exit-site appearance is summarized in Table 30-6.[74] An exit-site infection is present if there is purulent discharge at the peritoneal catheter exit-site or if the exit site appearance score is higher than or equal to 4. The presence of induration and tenderness indicate poor prognosis.[161] It should be noted that isolated erythema can represent either skin irritation or an early infection.

A catheter tunnel infection is defined as the presence of pain, tenderness, erythema, induration, or any combination of these signs and symptoms present over the subcutaneous tunnel of the catheter. Nevertheless, catheter tunnel infections are commonly occult and often only detected by ultrasonography of the subcutaneous catheter tunnel.[22,162] Tunnel infections occasionally occur in the absence of an exit-site infection.[22,162] However, it is present in approximately half of all exit-site infections as detected by the use of ultrasonography. The infection can involve the outer cuff, the inter cuff, or the inner cuff of the catheter.[22,162] As the infection spreads along the tunnel toward the peritoneum, the risk of peritonitis increases.[22,162]

TABLE 30-6 Scoring System of Exit Site Appearance in Peritoneal Dialysis

	0 POINT	1 POINT	2 POINTS
Swelling	No	Exit only; <0.5 cm	>0.5 cm and/or tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain	No	Slight	Severe
Drainage	No	Serous	Purulent

NB. Infection should be assumed with exit site score of 4 or greater. Purulent discharge, even if alone, is sufficient to indicate infection.
Data from B. Piraino, G.R. Bailie, J. Bernardini, et al., Peritoneal dialysis-related infections recommendations: 2005 update, Perit. Dial. Int. 25 (2005) 107–131.

Risk Factors

The major risk factor in *S. aureus* catheter infections is carriage of *S. aureus*.[110,163] Approximately 50% of new and prevalent PD patients are *S. aureus* carriers.[163] In approximately one-third of them, repeat cultures revealed carriage of the same phage type; in 16%, either only one culture was positive or subsequent culture was positive but showed a change in phage type with time.[163] Patients who were *S. aureus* carriers had significantly higher incidences of *S. aureus* exit-site infections, tunnel infections, and peritonitis than patients who were not carriers.[110,163]

Intravenous (IV) antibiotics given at the time of catheter insertion reduce infection risk.[4] Tunnel infections are probably more common in diabetic patients.[164] Immunosuppressed patients are at increased risk for catheter infections.[165] A downward-directed catheter exit site is associated with easier-to-treat infections, with fewer episodes of catheter-related peritonitis.[4]

Treatment

The treatment of exit site infections is summarized in Figure 30-2 and Table 30-7. Intensified local care with chlorhexidine or diluted hydrogen peroxide is often used together with systemic antibiotic therapy.[57,58] Local antibiotic, such as mupirocin or gentamicin cream, is sometimes used without concomitant systemic antibiotics for an exit site with an equivocal appearance or when only erythema is present.[166]

Oral antibiotic therapy for catheter infection should be tailored according to the specific organism identified. *S. aureus* catheter infections are treated with antibiotics such as penicillinase-resistant penicillin or trimethoprim-sulfamethoxazole.[161,166] Exit site care is intensified. Rifampin may have activity within bacterial biofilm and can be used as additional therapy, although it should not be used alone. Oral antibiotics appear to be as efficacious as parenteral agents.[166] In view of the growing concern about vancomycin-resistant enterococci, this agent should not be used to

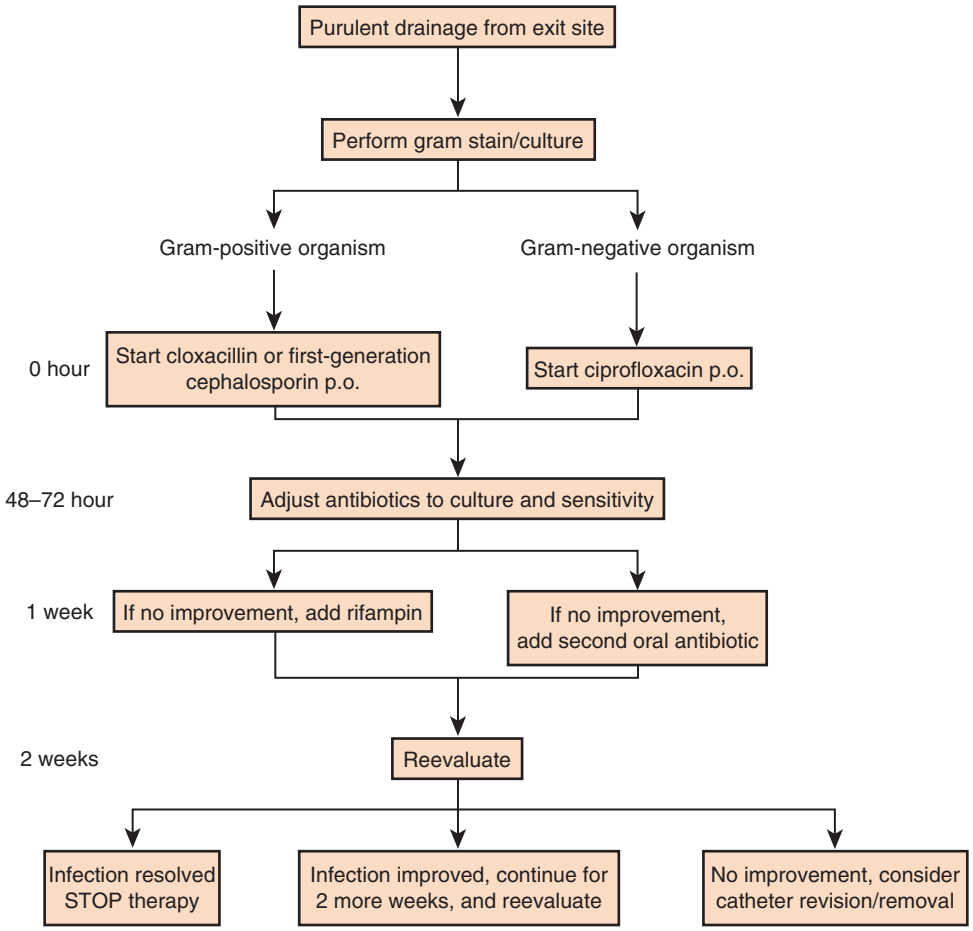


FIGURE 30-2 Flow chart for diagnosis and management of exit-site infections. (From W.F. Keane, G.R. Bailie, E. Boeschoten, et al., Adult peritoneal dialysis related peritonitis treatment recommendations: 2000 update, Perit. Dial. Int. 20 (2000) 396-411.)

TABLE 30-7 Protocol Options to Prevent Exit-Site Infections

1. Exit-site mupirocin:
a. Daily after cleansing in all patients
b. Daily after cleansing in carriers only
c. In response to a positive exit-site culture for *S. aureus* denoting carriage
2. Intranasal mupirocin twice per day for 5 to 7 days:
a. Every month, once patient is identified as a nasal carrier
b. Only in response to positive nose culture
3. Exit-site gentamicin cream daily in all patients after cleansing

Data from B. Piraino, G.R. Bailie, J. Bernardini, et al., Peritoneal dialysis-related infections recommendations: 2005 update, Perit. Dial. Int. 25 (2005) 107–131.

treat exit-site or tunnel infections unless the infecting organism is methicillin resistant.

Prolonged antibiotic therapy (over 2 weeks) is often necessary for *S. aureus* catheter infections.[167] Effectiveness of antibiotic therapy for *S. aureus* tunnel infections may be assessed and further therapeutic decision guided by repetitive ultrasonography of the tunnel.[165] In a study of deep tunnel infection without peritonitis caused by *S. aureus*,[165] sonographic examination of the tunnel was performed every second week. If the hypoechogenic area around the cuff decreases for 30% or more, conservative treatment with antibiotic therapy had an 85% success rate. In another study, sonolucent zone around the external cuff over 1-mm thick following a course of antibiotic treatment and the involvement of the proximal cuff are associated with poor clinical outcome.[168] In the latter study, catheter infection caused by Pseudomonas aeruginosa, the clinical outcome was uniformly poor irrespective of the sonographic findings.[168]

Antibiotic therapy is generally prescribed for bacterial colonization or collection around the catheter external cuff. Surgical revision of the exit site and tunnel, with removal of the external cuff, and exposure of the infectious portion of the catheter tunnel may be considered.[169] In selected cases, cuff-shaving may be considered as the alternative to catheter replacement for tunnel infection.[170] However, the procedure is associated with a risk of immediate peritonitis and should not be attempted without systemic antibiotics coverage. Revision of the tunnel and exit site is contraindicated if the deep cuff is involved or if simultaneous peritonitis is present. If the inner cuff is involved with the infection, as demonstrated by ultrasonography of the tunnel, the catheter should be removed because peritonitis is likely to develop within weeks in untreated cases.[22] In addition, if the response to antibiotics is inadequate, it is appropriate to replace the catheter in a single procedure.

PREVENTION

There are several approaches to reduce the risk of peritonitis. Despite much enthusiasm, no particular catheter has been definitively shown to be better than the standard silicon Tenckhoff catheter for prevention of peritonitis. Catheter

types using downward and lateral tunnel-tract and exit-site configurations produce equivalent outcomes for infectious and mechanical complications.[171] The risk of touch contamination at the time of the exchange has decreased, owing to the improvement in connection technology. Peritonitis rate is improved after the introductions of various disconnect systems.[13–15] The fundamental concept of the disconnect system is "flush-before-fill," which carries with it any contaminating bacteria introduced during connection.[172,173] A recent systematic review concludes that of all catheter-related interventions designed to prevent peritonitis in PD, only disconnect (twin-bag and Y-set) systems have been proved to be effective (compared with conventional spike systems).[174] There seems no obvious difference in peritonitis rate between various twin-bag systems.[15,175] As to the type of PD solution, peritonitis risk appears to be similar among glucose, icodextrin, and amino-acid based solutions.[176] There is early evidence that bicarbonate-buffered dialysate may reduce the peritonitis risk, as compared to conventional lactate-based solution,[66] but further confirmatory studies are needed.

Careful selection of patients and an emphasis on training also diminish the rate of peritonitis secondary to contamination. Prowant[177] outlines the importance of nursing intervention in the prevention of peritonitis. Training by experienced nurses is the key to keep peritonitis rates low. Continued monitoring of peritonitis rate is necessary in a dialysis program so that intervention can be made if peritonitis rates are problematic.[178] Peritonitis rates should be less than one episode per 18 patient-months; a higher rate of peritonitis should be followed by a critical appraisal of the pathogenetic organisms and the training program, so that an intervention to reduce rates can be implemented. For patients with recurrent peritonitis, retraining of dialysis exchange, with reinforcement of antiseptic procedures, may be advisable. A recent multicenter observational study suggests that retraining would be particularly important for younger patients (less than 55 years old), patients with lower education level, and patients in the early or late phase of PD therapy (less than 18 months or more than 36 months).[179]

Patients with *S. aureus* nasal carriage and all immunosuppressed patients are at high risk for *S. aureus* infections.[165,180] The rate of such infections may be reduced with prophylactic antibiotics. Antibiotic prophylaxis with mupirocin applied at the exit site[181] or intranasally[182] or with oral rifampin[183] reduces the risk of *S. aureus* catheter infection. In general, we prefer mupirocin because rifampin prophylaxis is associated with side effects and may result in resistant organisms.[181,183] Repetitive courses are needed if either intranasal mupirocin or rifampin is used, because recolonization is frequent.[183] A systematic review of randomized controlled trials concluded that nasal mupirocin reduces exit-site and tunnel infection but not peritonitis.[184] Alternatively, gentamicin cream may be considered. In a randomized, double-blind control trial of 133 PD patients, Bernardini and colleagues[185] found that, as compared to daily mupirocin ointment, gentamicin cream applied daily to the peritoneal catheter exit site reduced Pseudomonas aeruginosa and other gram-negative catheter infections (0 versus 0.11 episode per year) and reduced peritonitis by 35%, particularly gram-negative organisms (0.02 versus 0.15 episode per year).[185] In this study, gentamicin cream was as effective as mupirocin in preventing *Staphylococcus aureus* infections. Another randomized controlled trial found that a regimen of one single-strength tablet of trimethoprim-sulfamethoxazole on alternate days resulted in fewer staphylococcal peritonitis episodes, especially of those caused by *S. aureus*, with the most prominent effect during the first 3 months of therapy.[186] However, we have to be aware of the potentials for developing resistance with long term prophylaxis. Transmission of MRSA among dialysis patients, healthcare workers, and patients family members in a dialysis unit is possible.[187] Monitoring and eradication of MRSA from patients, healthcare workers, and their family members should be considered to prevent continuous spread between healthcare facilities and the community.[187] A summary of the protocol options for preventing exit-site infection is outlined in Table 30-7.

Prophylactic antibiotics administered at the time of insertion decrease infection risk. In general, single-dose cefazolin immediately before catheter insertion is sufficient. However, Gadallah and colleagues[188] found that single-dose vancomycin is superior to single-dose cefazolin in reducing the risk for postoperative peritonitis, and vancomycin should be considered in high-risk cases. A systematic review of randomized controlled trials concluded, based on four studies, that preoperative intravenous antibiotic prophylaxis reduces early peritonitis, but not exit-site and tunnel infection.[184] Prophylactic antibiotic therapy with adequate coverage of gram-negative organism is recommended before a colonoscopy or similar interventions because the procedure can lead to gram-negative peritonitis. A recent retrospective study found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3%, whereas colonic biopsy or polypectomy did not appear to further increase the risk.[189] In this study, there was no peritonitis after colonoscopy in patients that were given antibiotics for prophylactic purposes, although the difference was not statistically significant.[189]

The use of povidone-iodine ointment at the exit-site prevents exit site infections during the first 20 weeks of PD. Catheter immobilization, proper location of the exit site, sterile wound care immediately after placement of the catheter, and avoidance of trauma are all preventive measures recommended by most authorities.[190] Downward-pointing exit-site locations, suggested as a method of reducing exit-site infections, decrease the risk of catheter-related peritonitis.[4,191] Although new catheter designs or modifications have been proposed as a means of reducing peritonitis from catheter insertion, results of clinical trial are largely disappointing. Subcutaneous burying of the distal catheter segment before starting PD does not reduce the risk of contracting peritonitis or exit-site infection,[192] and delayed use of the catheter actually may be associated with a greater risk of infection.[192] Surface modification of catheters with ion beam implantation of silver produced no clinical effect with respect to reducing dialysis-related infections.[193]

Studies in both children and adults have shown that the risk of *Candida* peritonitis can be reduced with prescription of oral nystatin or fluconazole during antibiotic therapy.[194,195] In another recent observational study, the fungal peritonitis rate of the nystatin group was slightly lower than that of the control group (0.011 vs 0.019 per patient-year), but the difference did not reach statistical significance.[196] There was, however, a significant decrease in the incidence and proportion of antibiotic-related fungal peritonitis in the nystatin group.[196] Patients requiring frequent or

prolonged antibiotic therapy benefit from such prophylaxis. Because oral nystatin is safe and inexpensive, we advocate routine prescription of oral nystatin during empirical antibiotic treatment for PD-related peritonitis.

Malnutrition is a well-known risk factor for peritonitis.[197] No study to date, however, specifically examines the benefit of nutritional intervention in reducing the risk of peritonitis. Although there are few published data, quality improvement programs with continuous monitoring of infections, both of the catheter exit site and peritonitis, are logically important to decrease the PD related infections in PD programs.[198] Continuous review of every episode of infection to determine the root cause of the event is advisable in any PD programs.[198]

The success of peritoneal dialysis depends in part the prevention and treatment of peritoneal dialysis associated infections. The need to prevent and treat the infections also requires resources like cost relating to the double bag system, the prophylactic, the therapeutic antibiotics, and the cost in removing the catheter, the need to switch to hemodialysis, and the need to reinsert another catheter.[199] Elderly patients, under skillful training and high quality PD programs, can also enjoy equally low peritonitis rate when compared to the young.[200] With good prevention and treatment of PD infections, we can help in reducing a lot of patient morbidity and even mortality in relation to the problem.

A full list of references are available at www.expertconsult.com.

Chapter 31

NONINFECTIOUS COMPLICATIONS OF PERITONEAL DIALYSIS

Ziv Harel, M.D., F.R.C.P.C and Joanne M. Bargman, M.D., F.R.C.P.C

Although peritonitis is regarded as the Achilles heel of peritoneal dialysis (PD), a number of serious noninfectious complications can develop in patients on PD. These complications can lead to significant morbidity and mortality. Some complications, such as hernias and dialysate leaks, are commonly encountered; others, such as encapsulating sclerosing peritonitis, are rare and can be devastating. This chapter will address these and other noninfectious complications of peritoneal dialysis.

COMPLICATIONS RELATED TO INCREASES IN INTRAABDOMINAL PRESSURE

The instillation of dialysate into the peritoneal cavity leads to an increase in intraabdominal pressure (IAP).[1,2] Two principal factors govern the magnitude of the rise in IAP: the volume of dialysate instilled and the position the patient assumes during the dwell.[1,2] A strong positive relationship exists between the amount of dialysate instilled into the peritoneal cavity and IAP. The effect of patient position is also important, with the supine position generating the lowest IAP for a given volume of dialysate.[3] Other factors that may increase IAP include increased body mass index and activities such as exercising, coughing, and straining.[2]

Hernia Formation

In accordance with Laplace law, the tension on the abdominal wall increases with instillation of dialysate as a result of the rise in IAP and the larger radius of the abdomen. Increased abdominal pressure and abdominal wall tension place mechanical stress on the supporting structures of the abdomen and can lead to hernia formation in those with congenital or acquired weakness or defects. The areas of weakness are probably very important in the pathogenesis of hernias.

Incidence, Types of Hernia, and Etiological Factors

The prevalence of hernia in PD patients has been reported to range from 10% to 25%.[4–6] A recent study has speculated that the prevalence of this condition may be even higher because of the presence of asymptomatic hernias that are not detected until a complication occurs.[5]

Umbilical hernia has been the most commonly described type of hernia occurring in PD patients.[5] However, a multitude of other types of hernia have been reported. These include: incisional hernia, inguinal hernia, ventral hernia, epigastric hernia, femoral hernia, Spigelian hernia, cystocele, Richter hernia, and herniation through the foramen of Morgagni.[4,7–11]

Numerous risk factors for hernia formation exist including older age, female sex, multiparity, midline PD catheter insertion, and having undergone a previous hernia repair (Table 31-1).[10] Moreover, some studies have demonstrated a correlation with an increased body mass index (BMI), whereas others have reported the opposite effect.[2,12,13] Continuous ambulatory peritoneal dialysis (CAPD), rather than night-cycler-based dialysis, has also been reported as a risk factor for hernia, possibly the result of an increased duration of time spent upright leading to sustained increased IAP.[10] Finally, polycystic kidney disease can predispose PD patients to hernia

TABLE 31-1 Risk Factors for Hernia Formation
Large dialysate volumes
Sitting position
Valsalva maneuver (during activities, e.g., exercise)
Recent abdominal surgery
Deconditioning
Multiparity
Pericatheter leak
Obesity
Congenital anatomical defects
Polycystic kidney disease

development through multiple mechanisms, including higher IAP caused by the enlarged kidneys, a patent processes vaginalis, or as a manifestation of a generalized connective tissue disorder leading to weakening of the abdominal wall.[14,15]

Clinical Presentation and Diagnosis

Typically hernias present as a painless swelling. This may occur after an antecedent event such as a coughing bout or after physical exertion.[2] As previously mentioned, some hernias may be clinically occult and present less commonly with diminished effluent return or abdominal edema resulting from dialysate leak through defects in the abdominal wall.[16]

The most worrisome complications of hernia are incarceration and strangulation of bowel.[17] While this may occur through any kind of hernia, those with small umbilical hernias seem to be most at risk.[11] Here patients may present with a tender lump, recurrent episodes of peritonitis with multiple gram negative organisms, and signs and symptoms of bowel obstruction.[8]

Diagnosing hernia is usually straightforward in the correct clinical setting. However, hernias may also be clinically occult. Physical examination maneuvers aimed at increasing IAP thereby making the hernia more obvious can be unhelpful, and therefore ancillary tests may be necessary to diagnose or confirm the hernia.

Ultrasonography is an excellent modality to distinguish pericatheter hernias from masses caused by hematomas, seromas, or abscesses.[18] With ultrasound, hernias are often solid-appearing, whereas the other conditions are characterized by fluid collections.[18]

While ultrasound is helpful in detecting pericatheter hernias, computed tomography (CT) scanning is the most sensitive and specific modality to delineate other hernias.[19] The diagnostic utility of CT scanning is improved by the use of intraperitoneal dye.[19] Typically, 100 ml of dye is added to the dialysate, which is infused into the peritoneal cavity.[20] The patient should remain ambulatory over the next 2 hours to facilitate the entry of peritoneal fluid containing the dye into the hernia sac and any other potential areas of leak. CT scanning is then performed (Figure 31-1).

Radionuclide scanning has also been used in the diagnostic workup of hernias. Radioligands such as DTPA, albumin colloid, and tin colloid at a dose of 1–5 millicuries (mCi) are injected into 0.5 to 2 L of dialysate.[21] The patient is asked to sit up and lean forward to increase IAP and hence to encourage the radiolabelled dialysate into the leaking sites.

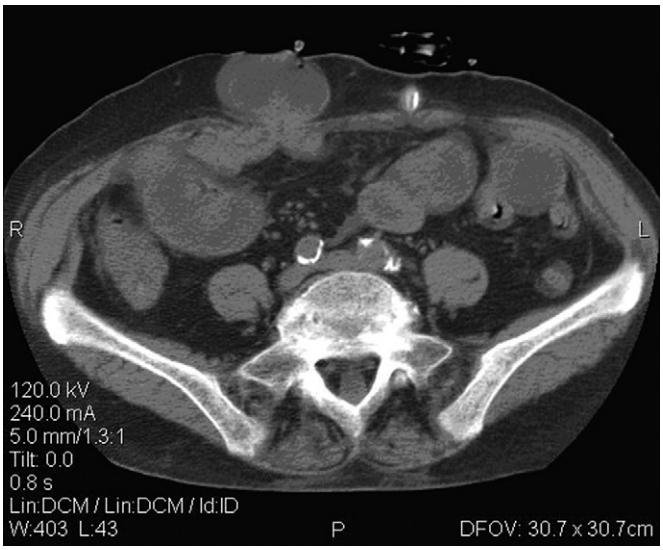


FIGURE 31-1 CT scan of incarcerated ventral hernia in a PD patient. (Courtesy of Dr. Joanne Bargman.)

Subsequent scanning by gamma camera can then track the path of the dialysate. The total dose of radiation is a fraction of that originally instilled into the peritoneal cavity as much it drained out of the body with the dialysate.[21]

Magnetic resonance imaging (MRI) has recently been used to diagnose hernias associated with abdominal wall and genital leaks.[22,23] This modality is beneficial in that dialysate is used as the "dye" thereby making it devoid of ionizing radiation. Furthermore, MRI will detect where dialysate is residing in the soft tissues, whereas CT scanning will only pick up what has leaked since instillation of the dye.

Treatment

The vast majority of patients on PD who develop a hernia should undergo surgical repair. A notable exception is those individuals who are an unacceptably high surgical risk. In these patients, however, the development of a hernia does not necessarily obviate the use of PD.[24] In fact, PD may be continued if the patient uses methods to lower IAP such as dialysis while supine, lower dialysate volumes, and wearing an abdominal binder for external support.

While hernias may be cosmetically unappealing, most should be repaired to prevent the serious complications of bowel incarceration and strangulation. This is particularly the case for smaller umbilical hernias.[25] In contrast, ventral hernias carry little risk of strangulation, but the defect in the abdominal wall integrity associated with these hernias serves as a source of dialysate leak leading to formation of abdominal edema.[25]

In PD patients whose hernia will be surgically repaired, three guiding principles should be followed to ensure excellent outcomes:[26]

1. Ensure that the patient is fit for surgery.
2. Avoid prolonged disruption of PD that would necessitate the use of hemodialysis.
3. Use techniques of surgical repair that minimize the chance of recurrence in this high-risk population.

Recent reports have demonstrated that PD patients undergoing hernia repair need not be automatically

TABLE 31-2 Protocol for Peritoneal Dialysis (PD) Before and After Hernia Surgery

- Continue on standard PD therapy until the morning of surgery
- Drain the PD fluid prior to the surgery
- No dialysis for the first 48 hours
- Laboratory investigation at start of IPD and weekly
- IPD 3 times per week (1-L exchange × 10 for 10 hours) for 2 weeks for CAPD patients and for 1 week for CCPD patients
- CAPD patients resume low volume (1-1.5 L × 5 exchanges for 2 weeks)
- CCPD patients to continue on NIPD for 4 more weeks
- All patients resume preoperative PD prescription after 4-5 weeks

(From H. Shah, M. Chu, J.M. Bargman, Perioperative management of peritoneal dialysis patients undergoing hernia surgery without the use of interim hemodialysis, Perit. Dial. Int. 26 [6] [2006] 684–687.)
CAPD, continuous ambulatory PD; *CCPD*, continuous cycling PD; *IPD*, intermittent PD; *NIPD*, nocturnal intermittent PD.

converted to hemodialysis (HD).[24,27] These patients can continue standard PD therapy until the morning of surgery, drain the PD fluid before surgery and withhold dialysis for the first 24 to 48 hours after surgery. Dialysis can then be safely reintroduced using the principles of low IAP (low volumes using a night cycler and day dry) for a 2 week duration. The theoretical concerns regarding electrolyte abnormalities and transient underdialysis have not been demonstrated in a single-center retrospective study.[24] In patients with significant residual renal function, this is even less of a concern. Temporary transfer to HD should be initiated when the hernia is associated with bowel strangulation, which may compromise the bacterial barrier of the bowel wall and subject the patient to peritonitis. An example of a management strategy for PD before and after hernia surgery is outlined in Table 31-2.

Recurrence of surgically repaired hernias in PD patients has been reported to be as high as 27%.[11,28] To minimize the risk of recurrence, patients should be counseled on avoiding activities that could lead to transient elevations in IAP upon recommencement of PD. Furthermore, the use of an overlying polypropylene mesh to reinforce the hernia repair following conventional hernioplasty has also been demonstrated to minimize recurrence.[5] The mesh does not appear to be vulnerable to becoming infected secondary to a subsequent occurrence of peritonitis.[29] The options for patients who have multiple recurrences of hernia include: 1) night-time cycler dialysis with smaller daytime volumes, or 2) transfer to HD.

Dialysate Leaks

The loss of dialysate from the peritoneal cavity, either into another compartment or around the PD catheter itself, is known as a peritoneal dialysate leak. This phenomenon is often a consequence of the loss of peritoneal membrane integrity caused by a defect within the membrane. It may manifest with a wide spectrum of presentations: from moisture around the PD catheter to genital and abdominal wall edema. The ramifications of dialysate leaks are quite serious and distressing as they may lead to technique failure.[16]

Incidence, Classification of Leaks, and Risk Factors

The incidence of dialysate leaks varies widely in the literature. Conservative reports demonstrate an incidence of 5% in CAPD patients; however, others have noted rates as high as 10%.[16,30] The variability in incidence may be the result of inhomogeneity in the reporting of leaks.

Dialysate leaks may be classified as early or late depending upon the time course they develop after PD catheter insertion (Table 31-3). Early leaks are those that develop within 30 days of catheter insertion.[16,30] They are usually related to catheter placement and present as dialysate leakage at the exit site or incision. In contrast, late leaks are most often related to a defect in the peritoneal membrane.[16,30] These leaks more often present with hydrothorax, genital, and abdominal wall edema.

TABLE 31-3 Comparison Between Early and Late Dialysate Leaks in PD Patients

	EARLY LEAKS	LATE LEAKS
Pathogenesis	Poor tissue healing Median catheter insertion Onset of CAPD immediately after catheter insertion	Poor tissue healing/tensile strength Straining, infections, hernias Method of catheter insertion may have an effect
Manifestations	Usually external leaks	Usually leaks into tissues
Diagnosis	Usually by clinical means	Often requires imaging
Management	CAPD interruption alone often effective Surgery frequent	Usually requires surgery Occasionally conservative means (change to other modality of peritoneal dialysis, observation) are sufficient
Outcome	Catheter loss frequent Permanent discontinuation of CAPD improbable	Catheter loss frequent Permanent discontinuation of CAPD for conditions associated with the leak probable
Prevention	Paramedian surgical insertion with meticulous closure of the peritoneum and obliteration of all potential open tunnel spaces. Waiting period for 10-14 days between catheter insertion and onset of CAPD Starting CAPD with low volumes Peritoneoscopic insertion is an alternative to paramedian insertion Avoiding heavy straining Prevention of infections	Same as easy leak pervention. Research is needed in the area of improving tissue healing/tensile strength.

(From A.H. Tzamaloukas, L.J. Gibel, B. Eisenberg, et al., Early and late peritoneal dialysate leaks in patients on CAPD, Adv. Perit. Dial. 6 [1990] 64–71.)

The risk factors for the development of leaks are similar to those for hernia development. However, early leaks can be the result of not placing a secure purse-string sutures around the deep cuff of the catheter.

Complications of Dialysate Leaks

1. Genital Edema Genital edema is one of the most distressing complications of PD. It has been described to occur in up to 10% of CAPD patients.[31] Women have been noted to have a lower incidence of genital edema compared to men, which has been attributed to the processus vaginalis being patent more often in males.[32]

Two mechanisms have been proposed to explain the formation of genital edema.[31] First, dialysate can track through a patent processus vaginalis into the labia or scrotum, leading to a hydrocele of dialysis fluid. Along with dialysate, bowel can also migrate along the processus vaginalis into the scrotum, leading to a concurrent and often occult indirect inguinal hernia.[33] The second mechanism leading to genital edema is imparted by defects in the abdominal wall, particularly at the catheter insertion site. These defects allow dialysate to track inferiorly along the abdominal wall, leading to edema of the scrotum and foreskin (Figure 31-2).

The diagnosis of genital edema is usually obvious as it is quite painful and distressing for the patient. That being said, it is important to rule out other processes that may lead to local inflammation, particularly in males, such as epididymitis. Sometimes, the patient may misinterpret the development of genital edema as indicative of general fluid overload and attempt to ultrafilter more fluid. They may complain of diminished effluent return, which in this case is the result of ongoing dialysate leak.

CT scanning is the modality of choice to delineate the cause of the genital edema.[19,34,35] The technique is similar to that used for the detection of hernias with dye being instilled into the peritoneal cavity with the dialysate. The subsequent scan, if positive, will show the movement of dialysate through a patent processus vaginalis or abdominal wall defect into the scrotum or labia. Radionuclide scanning may also be used, with 3–5 mCi of technetium-labeled albumin colloid injected into the dialysate and infused into the patient.[36,37]

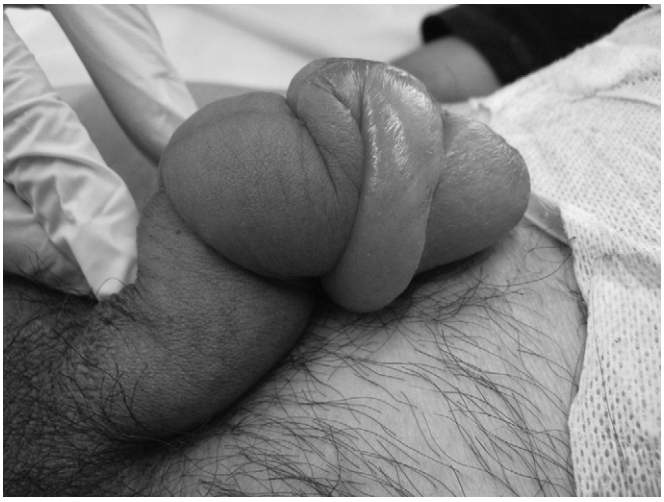


FIGURE 31-2 Genital edema in a patient on PD. (Courtesy of Dr. Joanne Bargman.)

The initial steps in the management of genital edema should address the risk factors leading to fluid accumulation in the genitals. Specifically, measures aimed at decreasing IAP and minimizing fluid translocation along low-resistance pathways, such as the processus vaginalis, should be undertaken.[31] In this regard, a conservative approach is used, which involves the discontinuation of CAPD, bedrest, scrotal elevation, and the initiation of continuous cyclic peritoneal dialysis (CCPD) or nocturnal intermittent peritoneal dialysis (NIPD) using low volumes with the patient supine.[16,30] This is done for approximately 1–3 weeks.[38] The success of this approach is usually dependent on having adequate residual renal function to compensate for the decrease in adequacy. If the patient does not have adequate residual renal function, they should receive hemodialysis temporarily while waiting for the edema to dissipate and surgical repair of the defect. One center's experience with this approach noted only a 14% rate of recurrence of genital edema.[30]

If conservative treatments fail, surgical repair can be undertaken. In these cases, the same preoperative and postoperative principles as hernia repair apply.

2. Abdominal Wall Edema Similar to genital edema, abdominal wall edema is usually a complication of a late dialysate leak. The incidence of abdominal wall edema is not well-defined in the literature; however, it is believed to occur less frequently than hernias.[16]

The presence of abdominal wall edema suggests that the origin of the peritoneal defect is located within one of the following sites: the incisional site for the insertion of the PD catheter, the catheter tunnel and exit site, from a soft-tissue defect within a hernia, or from a peritoneal-fascial defect.

Abdominal wall edema may be difficult to detect clinically because it may present with nonspecific signs and symptoms. These include diminished effluent returns and weight gain because of dialysate accumulating in tissues of the abdominal wall. Other presenting features include abdominal asymmetry or increased abdominal girth. Patients with suspected abdominal wall edema should be examined while standing to better detect any abdominal asymmetry. Inspection of the abdomen may reveal it to look pale and boggy with indentations made by the waistband of underpants or the catheter itself.

Investigating abdominal wall edema uses the same imaging studies as for genital wall edema. CT scanning using dye-labeled dialysate has demonstrated efficacy in confirming edema and the site of the leak.[19,20,34,35] Likewise, isotopic scanning can also be used. Again, it is important to let the patient ambulate for at least 2 hours after the instillation of the dye/isotope to facilitate its movement into the abdominal wall. MRI scanning has also been used, with one study revealing better delineation of dialysate movement than with CT.[23] This finding is likely because MRI will detect dialysate residing in soft tissue, whereas CT will only detect dialysate that has leaked over the course of the study.

The principles of management of abdominal wall edema are similar to those of genital edema (see previous discussion). In brief, the dialysis regimen is converted to CCPD in the supine position with low volumes. The goal is to allow the abdominal wall defect to heal on its own. Should this fail to occur, surgical intervention to close the defect is

undertaken. If the leak is from a hernia, the hernia should be repaired.

3. Pericatheter Leak As previously mentioned, pericatheter leak is an early form of dialysate leak, often presenting in PD patients who are initiated on CAPD almost immediately after insertion of their catheter. The risk factors for this condition are similar to those of hernia and have been highlighted previously.

Typically pericatheter leaks are clinically obvious, presenting as wetness around the catheter exit site, or wetness of the exit-site dressing. The diagnosis can be proven using similar CT techniques as for hernias, genital, and abdominal wall edema.[19,20]

The treatment of these leaks differs from that for abdominal wall and genital edema. Here the patient should be drained of dialysate and PD should be discontinued for at least 48 hours.[16] Sometimes this yields enough time for the leak to seal; however, should this not be the case, then the patient should commence hemodialysis for a few days if dialysis is needed. If this fails to abrogate the leak, then the catheter should be removed and reinserted at a different site. Overall, leaks have required catheter replacement in 37%-48% of patients.[30,39] Other interventions aimed at sealing the leak, including the placement of pursestring sutures or fibrin glue around the cuff after the fact have not been efficacious.[40] A stitch should never be placed at the exit site. The source of the leak is where the catheter exits the peritoneal cavity, so exit-site stitches will only mask the problem.

While dialysate leak at the exit site increases the risk of peritonitis or tunnel infection, the use of prophylactic antibiotics is usually not warranted unless there are signs of obvious infection.[39]

Prevention of Dialysate Leaks

Preventive strategies to reduce the incidence of dialysate leaks have not been formally studied. Having said that, an approach aimed at risk factor reduction has been advocated. Historically, the most important strategy to reduce early leaks is to delay the onset of CAPD for at least 14 days after catheter insertion.[41,42] However, it has recently been demonstrated that earlier break-in periods can be used without increased incidence of leaks.[43,44] It is important to use low volumes of dialysate if PD is to be initiated after a short or no break-in period to reduce the risk of pericatheter leakage.[45] Other preventive measures include the use of the paramedian surgical approach rather than a median approach when inserting catheters; however, this practice has also come under scrutiny recently.[46–49] Failed transplant patients are probably at increased risk of leak given the usual long history of corticosteroid use. Steroid use should be minimized and sirolimus discontinued before catheter insertion.[50]

Hydrothorax

Increased IAP can also lead to the translocation of dialysate from the peritoneal cavity across the diaphragm and into the pleural space. The accumulation of dialysis fluid in the pleural space is called hydrothorax (Figure 31-3).[51] This complication can occur almost immediately or as a late leak.

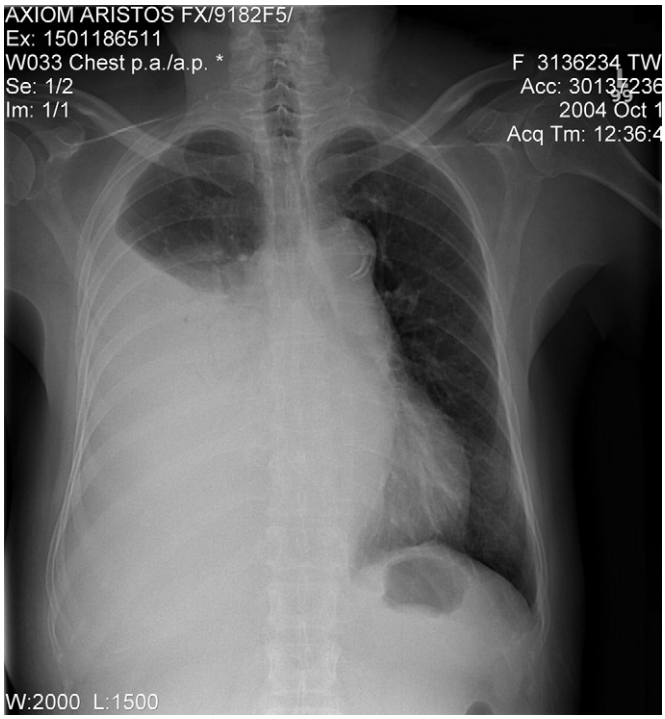


FIGURE 31-3 Right-sided PD hydrothorax. (Courtesy of Dr. Joanne Bargman.)

Pathogenesis

The pathogenesis of hydrothorax formation in PD patients has not been clearly elucidated. It has been speculated that two factors, possibly occurring concurrently, may be involved in hydrothorax development. These are 1) diaphragmatic defects combined with a large pleuroperitoneal pressure gradient and 2) abnormalities in lymphatic drainage.[52]

1. Diaphragmatic Defects Combined with a Pleuroperitoneal Gradient To allow the flux of dialysis fluid from the peritoneal cavity into the pleural space, a defect in the diaphragm, acting as a source of communication between the two spaces, must be present. However, it is not enough to have a defect; a pressure gradient must also exist between the two compartments to create a driving force for the movement of fluid. Here higher IAP created by the instillation of dialysate combined with the negative pressure in the pleural space leads to a pressure gradient favoring fluid movement from the peritoneum into the pleura.

Fluid will continue to move into the pleural space until there is equalization of pressure between the two compartments or there is an impediment to further movement. It has been postulated that a valvelike defect in the diaphragm or the action of the hepatic capsule to tamponade backflow of dialysate from the pleural to peritoneal space may be such impediments.[52]

Other than a peritoneal-pleural gradient, one or multiple defects in the diaphragm must be present to allow hydrothorax formation. These defects may be congenital or acquired. The nature of the underlying defect may explain why some individuals develop hydrothorax with their first-ever infusion of dialysis fluid.

From a pathological point of view, it has been noted that anomalies in the formation of the diaphragm can lead to defects and herniations of this structure. Autopsy studies have revealed localized absence of muscle fibers in the hemidiaphragm, which are replaced with a disordered network of collagen.[53,54] This collagen network is more susceptible to rupture when exposed to high pressures such as those provided by the instillation of dialysate. Moreover, when hydrothorax has been investigated by surgery, "blisters" or "blebs" have sometimes been noted on the pleural surface of the diaphragm.[53] With the instillation of dialysate into the peritoneal cavity, these blebs can be seen to swell and even rupture, thus providing a pathway to the movement of fluid.[53]

Patients presenting with hydrothorax months to years after PD initiation probably have an acquired defect of the diaphragm. Their attenuated diaphragmatic tissue is likely the consequence of ongoing injury from repeated exposure to raised IAP or recurrent episodes of peritonitis.[55,56]

2. Abnormalities in Lymphatic Drainage or the "Lymphatic Transfer Theory" The "Lymphatic Transfer Theory" was proposed to explain the contribution of impaired lymphatic drainage to the formation of hydrothorax in PD patients.[57,58] Based on surgical findings, this theory suggests that in susceptible individuals, the instillation of dialysis fluid leads to engorgement of the phrenic lymphatic system resulting in the transudation of fluid into the pleural space. While plausible, this mechanism cannot explain all cases of hydrothorax formation. Therefore, abnormalities in phrenic lymphatic drainage likely play a contributing rather than causal role in hydrothorax formation.

Incidence and Risk Factors

The incidence of hydrothorax in patients receiving PD has been reported to be 2%.[59] Similar to hernias, it has also been speculated that this figure is an underrepresentation of the true incidence of hydrothorax as the result of asymptomatic cases.[60]

Multiple risk factors for the development of hydrothorax in PD patients have been described in the literature.[52,53,55,56,59,61,62] However, it is interesting to note that in most cases of hydrothorax a risk factor is not identified.[14,59,63,64]

Polycystic kidney disease (PCKD) has been consistently associated with hydrothorax formation.[61] Two potential explanations for this correlation are 1) the polycystic kidneys compound the rise in IAP when dialysate is infused into the peritoneal cavity, and 2) there is a greater inherent weakness of the diaphragm as a part of a generalized connective tissue defect seen in this condition.[61]

Another important risk factor for hydrothorax is peritonitis.[59,62] While the link between these two conditions is not clear, it has been postulated that peritonitis may contribute to the further weakening of attenuated diaphragmatic tissue, thereby making it more susceptible to increases in IAP.[62]

Women are also more likely than men to develop hydrothorax. The reason for this sexual predominance is unknown, although stretching of the hemidiaphragm from previous pregnancy contributing to its weakness has been suggested.[53] Transient rises in IAP caused by coughing, straining, and the use of abdominal corsets have also been implicated as risk factors.[52,55,56]

Clinical Presentation

Most commonly, patients with PD-associated hydrothorax present with increasing shortness of breath. The degree of dyspnea is often commensurate with the size of the effusion. Other reported symptoms include pleuritic chest pain, diminished effluent volume, hypotension, and even weight gain as a result of decreased ultrafiltration.

Sometimes patients may complain of worsening dyspnea despite using more hypertonic dialysate exchanges. In this regard, the hypertonic dialysate solution causes more ultrafiltration, which will create an even greater IAP. The increased IAP will lead to further flux of dialysate into the pleural space thereby worsening the dyspnea.

Moreover, as previously mentioned, it is not uncommon for hydrothorax to be clinically silent and only discovered incidentally during radiographic procedures done for some other reason.

Diagnosis

In the correct clinical setting, the diagnosis of hydrothorax in PD patients may be quite simple to make. Having said that, it is important to consider other causes of dyspnea in PD patients including congestive heart failure, parenchymal lung disease, and pulmonary embolism. Physical findings are consistent with pleural effusion and include absent breath sounds, a pleural friction rub, and stony dullness to percussion in the base of the affected lung. Chest x-ray demonstrates a pleural effusion that is often right-sided and layers out when the patient is placed in the decubitus position. The clinical scenario wherein a patient develops a large right-sided pleural effusion within the first few dialysis exchanges is strongly suggestive of hydrothorax.

Historically, thoracentesis with pleural fluid analysis has been the first step in the diagnosis of PD associated hydrothorax. As the pleural fluid is composed of dialysate, it should possess the same biochemical characteristics. That is, it should be a transudate, have a low LDH, and a low WBC count.[52,59] Because the glucose concentration in the dialysate solution is very high, the pleural glucose concentration in the hydrothorax should similarly be elevated. Typically, a pleural fluid glucose concentration 50 mg/dl greater than serum glucose concentration is 100% sensitive and specific for diagnosing PD associated hydrothorax.[65] However, cases with borderline glucose values are not uncommon. This may occur if the fluid has been left in the pleural cavity for many hours and is partially reabsorbed by the parietal lymphatics.

At times, the diagnosis remains in doubt despite adequate pleural fluid sampling. In these cases, it has been previously recommended to instill a dye, such as methylene blue, into the dialysis fluid and then subsequently sample the pleural fluid looking for a blue discoloration.[66,67] This technique has fallen out of favor over the past few years because it generates false negative results and also acts as a chemical irritant in the peritoneal cavity.[66]

In cases where thoracentesis is contraindicated or nondiagnostic, peritoneal scintigraphy can be used to demonstrate the pleuroperitoneal connection. In different studies, between 3 and 10 mCi of technetium-labeled macroaggregated albumin or sulphur colloid has been instilled into the peritoneal cavity along with the usual volume of dialysis

fluid.[68,69] The patient is instructed to move around to ensure adequate mixing of the radioisotope and dialysate and to raise the IAP. Subsequent scanning detects movement of the isotope above the hemidiaphragm.

Recently, CT enhanced with intraperitoneal dye has become the diagnostic modality of choice for PD associated hydrothorax.[70] The procedure is similar to that for other types of dialysate leaks.

Magnetic resonance imaging without the use of gadolinium has also been used to detect dialysate leaks into the pleural space.[23]

Management

Before commencement of definitive treatment, immediate treatment of hydrothorax must be undertaken if there is respiratory compromise. This involves an emergent thoracentesis, which often dramatically improves the patients' symptoms and provides pleural fluid for analysis.

Subsequent treatment is dictated by whether the patient chooses to continue on PD. If the symptoms of hydrothorax were quite distressing that the patient requests to be transferred to hemodialysis, then the communication between the peritoneal and pleural space is of no consequence and does not require further management once the effusion has resolved.

However, if the patient desires to continue on PD, then a multitude of treatment options are available including: conservative management with temporary interruption of PD, conventional pleurodesis, and surgical thoracotomy or video-assisted thoracoscopic (VATS) repair of the diaphragmatic defect.[60,71] The underlying goal of treatment is simple: prevent recurrence of hydrothorax through the closure of the diaphragmatic defect. As no guidelines exist for the management of hydrothorax in PD patients, it is unclear which approach confers the best long-term outcomes.

1. Temporary Interruption of PD (Conservative Management) There is a clear consensus that interruption of PD should be the initial step in the definitive management of hydrothorax. It is believed that the discontinuation of PD acts to reduce the size of the effusion and in some cases promote spontaneous resolution of the pleuroperitoneal communication. Discontinuation of PD should occur for a period of 2–6 weeks.[60,71] A temporary transfer to hemodialysis is often necessary, especially if the patient has limited residual renal function. Using this approach, one case series noted a 53% success rate in the return to long-term PD.[71]

Occasionally, patients who experience hydrothorax on CAPD are able to resume PD by cycler after only being treated with conservative measures (i.e., temporary interruption of PD). As previously mentioned, the main determinants of IAP are volume and position, and therefore a dialysis prescription emphasizing low-volume, supine-based dialysis should be initiated in these patients. While somewhat counterintuitive, the supine position is not conducive to fluid migration into the pleural cavity. One explanation is that the decrease in IAP afforded by the supine position more than compensates for the movement of fluid into the pleura when supine.[72]

2. Pleurodesis Pleurodesis is another option for repairing the pleuroperitoneal communication leading to hydrothorax. This method involves the instillation of a sclerosing agent into the pleural cavity, which causes an inflammatory reaction, leading to pleural fibrosis and subsequent obliteration of the diaphragmatic defect. No consensus has emerged regarding the optimal timing for pleurodesis.[71] Some have proposed using it concurrently with conservative measures, whereas others have advocated its use as a second-line measure after conservative treatments have failed.

Several agents have been used successfully for pleurodesis. These include talc, tetracycline, autologous blood, fibrin glue, and hemolytic streptococcal preparation OK-432.[73–76] The efficacy of one agent over another is unknown; however, talc and tetracycline have been used less frequently.[71] This is due to the pain and propensity for a large systemic inflammatory reaction that is associated with their use.

Different techniques for pleurodesis have been used to treat hydrothorax. Generally, the conventional approach where the agent is instilled blindly through a chest tube is not as effective as direct visualization and chest tube drainage.[60] However, it is best to seek consultation with a thoracic surgeon who has expertise in pleurodesis.

Some authors advocate for the resumption of PD as early as 10 days after pleurodesis.[60] In contrast, others favor a more conservative strategy opting to resume PD after 4–6 weeks. While it is currently unclear what the best approach is, the use of pleurodesis in the management of hydrothorax is associated with good long-term results. In fact, a large systematic review demonstrated 48% of patients treated with pleurodesis were able to resume long-term PD.[71]

3. Surgical Intervention Thoracotomy and more recently VATS have become the preferred modality to obliterate the diaphragmatic defect. At thoracotomy or VATS the pleuroperitoneal communication can be directly visualized.[77,78] The "blebs" in the diaphragm can often be seen and can be sutured and reinforced with Teflon patches.[53] It is recommended that 2–3 L of dialysate be infused intraoperatively at the conclusion of the procedure to ensure that there is no seepage of dialysate indicating an ongoing defect.

VATS treatment of hydrothorax has been associated with excellent long-term outcomes. In one study, 88% of patients were able to resume long-term PD without recurrence of hydrothorax.[71]

MALFUNCTION OF THE PERITONEAL CATHETER

Malfunction of the peritoneal dialysis catheter is one of the most common complications of PD occurring in up to 20% of patients.[79] This complication often manifests early in the course of PD and is highlighted by poor drainage from the catheter.

There are two types of catheter drainage problems: 1) "one-way obstruction," which involves adequate inflow but poor outflow; and 2) "two-way obstruction," which entails both poor inflow and outflow.

Insufficient outflow is one of the most common causes of catheter malfunction.[80] It is usually the result of obstruction around the holes in the intraperitoneal portion of the dialysis catheter. During instillation of dialysate, the increased pressure pushes away the obstruction and so inflow is preserved. However, with the negative Bernoulli force involved in

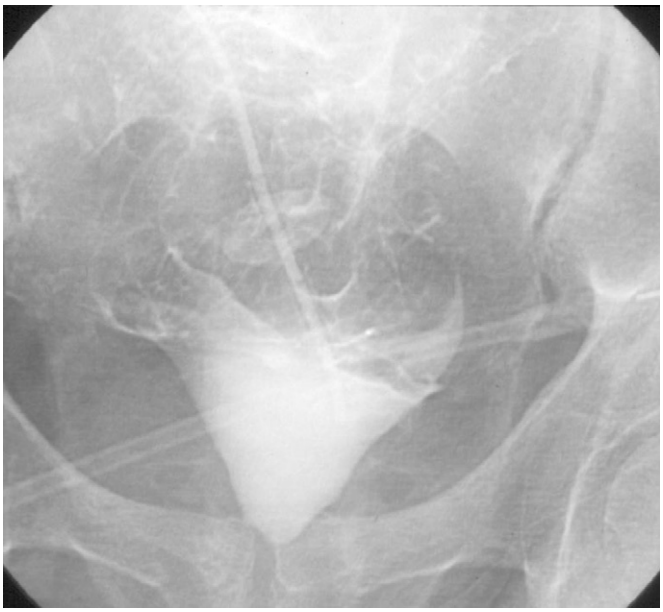


FIGURE 31-4 Compartmentalization of Dialysate Caused by Peritoneal Adhesions. A PD patient with prior intra-abdominal surgery experienced poor outflow from her PD catheter. A contrast study demonstrated a collection of dialysate in a "pocket" formed by adhesions from her previous surgery. (Courtesy of Dr. Martin Simons.)

drainage of effluent, the obstructing material comes into contact with the catheter and envelopes it, limiting outflow. A recent case series reported that catheter tip migration was the most common cause of one-way obstruction of the PD catheter.[81] Other causes of this complication include omental wrapping around the intraperitoneal portion of the catheter, and constipation whereby the stool-filled colon impinges on the catheter.[82,83]

Investigating for causes of poor outflow should always begin with an abdominal x-ray. This is a simple technique that allows for easy identification of the common causes of one-way obstruction, particularly constipation and catheter migration. If the abdominal film does not identify a cause, then a CT scan should be undertaken with contrast injected through the PD catheter. A catheter dye study can detect omental wrap or adhesions as causes of outflow obstruction (Figure 31-4).

The management of outflow obstruction is dependent on the cause. As constipation is a fairly common cause of outflow obstruction, it has been advocated that PD patients pay particular attention to their bowel movement frequency. Treatment with laxatives or sennosides is often effective in abrogating constipation and restoring catheter function.[84] It is also important to ensure that other potentially constipating medications such as iron and calcium be held temporarily before catheter insertion as these medications may contribute to constipation.

For catheter tips that have migrated into the upper abdomen, a guidewire can be inserted through the PD catheter and can bring it back into the pelvis.[85,86] Although successful repositioning will occur in almost all patients, the rate of recurrence is high, and patients will often need surgical manipulation.[81] Omental wrapping is usually dealt with surgically.[87]

Problems with both inflow and outflow, or "two-way obstruction" are usually the result of intraluminal obstruction or a kink in the PD catheter.[88] There have been multiple case reports highlighting materials that cause intraluminal obstruction. These include blood clots, cryoglobulins, fibrin strands, stones, and fungal balls.[89,90]

Before initiating a diagnostic workup for suspected "two-way obstruction" flushing the catheter under high pressure with heparinized saline followed by aspiration should be attempted.[91] If this maneuver is unsuccessful, then tissue plasminogen activator (tPA) should be instilled and allowed to dwell for a few hours to lyse old clots or other foreign material.[92,93] The transfer set should also be inspected to ensure it is not occluded with fibrin. If the catheter obstruction persists, then a diagnostic workup similar to that of "one-way obstruction" should be implemented. During this workup, if an occlusion or kink in the PD catheter is found, a rigid trocar can be inserted through the PD catheter to dislodge the occlusion and/or straighten the catheter. Should this be unsuccessful, surgical intervention may be required or the catheter may need to be removed and subsequently replaced.

HEMOPERITONEUM

Bloody dialysate or hemoperitoneum is a complication of PD that can be very distressing to the patient. As little as 2 ml of blood can render a 1 L bag of dialysate visibly blood-tinged.[94,95] Intraperitoneal bleeding may occur frequently in those not on PD; however, it is clinically silent. On the other hand, in patients on peritoneal dialysis, a window to the peritoneum is provided by the PD catheter, and therefore intraperitoneal bleeding is easily detectable.

The incidence of hemoperitoneum in PD patients is quite varied, ranging from 7% to 52% depending on the type of report.[96–98] The largest review to date demonstrated an incidence of 8.4% of PD patients.[96]

The majority of episodes of hemoperitoneum are the result of menstruation.[97,99] This is why women on PD are twice as likely as men to experience an episode of hemoperitoneum.[96] Two mechanisms have been proposed to explain the occurrence of blood in the peritoneal cavity associated with menstruation. First, uterine blood can be expelled retrograde by uterine contraction into the fallopian tubes that open into the peritoneal cavity. This process is known as retrograde menstruation.[100] Second, endometrial deposits in the peritoneal cavity may also cause bloody effluent. This is because this ectopic endometrial tissue is under the same hormonal control as the intrauterine endometrium and therefore sheds at the same time.[101]

While menstruation is the most common cause of hemoperitoneum in PD patients, a large number of other etiologies of this complication have been reported in the literature (Table 31-4). These include intraabdominal pathology of solid organs, vascular disorders, intraabdominal trauma, bleeding diatheses, intraperitoneal infections, and conditions such as encapsulating peritoneal sclerosis.[94,102–105] As some of these conditions may be quite serious, it is important to consider them in a patient presenting with bloody effluent.

The presentation of hemoperitoneum in a PD patient should initially trigger them to undertake several rapid PD exchanges to determine if the bleeding is persistent or is an acute event.[106] These exchanges are carried out using room temperature dialysate, which causes vasoconstriction of the intraperitoneal blood vessels and often abrogates the

TABLE 31-4 Causes of Hemoperitoneum

Catheter related
Obstetric and gynecological
Menstruation
Ovulation
Hemorrhagic luteal cyst
Ovarian cyst rupture
Pregnancy (uterine tear)
Intraabdominal
Kidneys
Renal cyst rupture
Acquired cystic kidney disease
Autosomal dominant polycystic kidney disease
Tuberous sclerosis (hamartomatous tumors)
Liver
Liver rupture
Hepatic tumors
Hepatocarcinoma
Hepatocellular adenoma
Liver metastasis
Liver cyst rupture
Spleen
Splenic rupture
Splenic infarct
Gastrointestinal tract
Vascular
Erosion of mesenteric vessel by Tenckhoff catheter
Aneurysm rupture
Procedure related
Pericardiocentesis
Radiation
Colonoscopy
Bleeding diatheses
Uremic platelet dysfunction
Anemia
Infection
Cytomegalovirus infection
Peritonitis
Other
Retroperitoneal hematoma
Iliopsoas spontaneous hematoma

(From S.Q. Lew, Hemoperitoneum: bloody peritoneal dialysate in ESRD patients receiving peritoneal dialysis, Perit. Dial. Int. 27 [3] [2007] 226–233.)

bleeding.[107] However, patients must be reminded to seek medical attention, especially if the bloody effluent persists or they develop symptoms of volume depletion.

The diagnostic evaluation of hemoperitoneum should be guided by the clinical setting. As menstruation is most often associated with this condition, an exhaustive workup for potential causes need not be undertaken in a menstruating female who is otherwise well. However, should this not be the case or should the hemoperitoneum persist, investigations must be undertaken to account for the source of the bleeding. At the very least, an abdominal ultrasound should be performed to assess for intraabdominal pathology. If this investigation is negative, then CT scan of the abdomen and pelvis should be performed. Routine blood work should also be undertaken including a complete blood cell (CBC) and a coagulation profile to assess for a coagulopathy. If the bleeding persists, despite negative radiographic investigations, then an isotope-labeled red blood cell (RBC) scan can be done to localize the site of bleeding.

The management of hemoperitoneum in PD patients is dependent on the underlying cause. As previously mentioned, a majority of patients will not require any definitive therapy; however, in severe cases of bleeding laparoscopy for both diagnostic and therapeutic reasons may need to performed.

In the majority of patients presenting with hemoperitoneum, there are often no long-term deleterious sequelae.[96,108,109] Specifically, studies have demonstrated that hemoperitoneum, be it a single episode or recurrent episodes, imparts no change on peritoneal membrane characteristics, ultrafiltration, or a predisposition of the peritoneum to peritonitis.[96,108,110]

That being said, the main complication associated with this condition is the coagulation of blood in and around the intraperitoneal portion of the PD catheter leading to its obstruction. Although this complication is uncommon, it is recommended that heparin be instilled intraperitoneally at a dose of 500 to 1000 Units/L as long as the dialysate has visible blood or fibrin, to prevent this problem.[63,94] Although administering anticoagulation in a patient having some degree of bleeding may appear counterintuitive, anecdotal accounts have demonstrated it to be efficacious in hemoperitoneum caused by menstrual bleeding.[109] When hemoperitoneum is a manifestation of other causes, the use of heparin needs to be weighed against the risk of increased bleeding.

ELECTROLYTE DISORDERS

Hypokalemia

Hypokalemia is the most common electrolyte abnormality encountered in PD patients. It is found in 10% to 36% of CAPD patients.[111] While the role of hypokalemia in producing arrhythmias and muscle weakness is well-documented, it has recently been found to be associated with increased mortality in Asian PD patients.[112] Moreover, hypokalemia could also induce a kaliopenic nephropathy, which may hasten the loss of residual renal function.[113]

Three processes have been postulated to explain the development of hypokalemia in PD patients: potassium loss through the bowel and dialysate, poor nutritional intake of potassium-rich fruits and vegetables, and intracellular shift of potassium.[112,114,115]

Previously, hypokalemia was ascribed to be the result of losses of potassium in the dialysate; however, a recent study has discounted this.[116] While dialysate losses of potassium are important, poor nutritional intake, particularly of potassium-rich foods, seems to be even more so. This is especially the case for certain ethnic groups who either avoid fruits and vegetables because of ethnocultural preferences or reduce the potassium content of foods substantially through traditional cooking methods.[112] Patients who have poor nutrition may also be catabolic. In this state, there is breakdown of intracellular macromolecular organic phosphates (RNA) into inorganic phosphates that are excreted in the dialysate, along with potassium. The result is hypokalemia, metabolic alkalosis, and hyponatremia.[114] Finally, potassium may be shifted into cells by a wide variety of mechanisms, particularly the stimulation of insulin secretion from the absorption of the dialysate glucose load.[117] It has recently been postulated that perhaps the lactate buffer added to dialysate solutions may also promote intracellular shift of potassium through a similar mechanism as insulin, that is, activation of the NHE3 antiporter creating a driving force for potassium to move into the cell. The role of

diuretics and residual renal function has been found to have very little impact on the development of hypokalemia.[112]

The management of hypokalemia in PD patients is often straightforward. As hypokalemia is a risk factor for cardiorespiratory dysfunction, potassium supplementation should be commenced to bring the serum potassium into the normal range. Food sources are preferred as first-line therapy and a dietician should be consulted. If nutritional intake fails to increase serum potassium concentration then oral potassium supplementation should be attempted. However, close monitoring of serum electrolytes is warranted, particularly in patients with limited renal reserve as it is not uncommon to find that a small amount of oral potassium supplementation can lead to a surprising increase in serum potassium concentration. Potassium chloride can also be added to the dialysate to diminish the concentration gradient for the diffusion of potassium into the dialysate to abrogate potassium loss, or can be added in high enough concentration to allow potassium to diffuse from the dialysate to the patient.[118] In the acute setting, up to 20 mmol/L can be added to the dialysate. This dose has been reported to increase the plasma potassium concentration by an average of 0.44 mmol/L over 2–3 hours.[111] However, given that the toxicity of the high intraperitoneal potassium concentrations is unknown; its use should be reserved for short-term emergency situations.

TABLE 31-5 Factors Implicated in the Etiology of Encapsulating Peritoneal Sclerosis

UNRELATED TO PERITONEAL DIALYSIS	RELATED TO PERITONEAL DIALYSIS
Idiopathic	Duration of PD
Inflammatory conditions	Peritonitis
Systemic lupus erythematosus	Acetate dialysis solutions
Familial Mediterranean fever	Chlorhexidine
Sarcoidosis	Plasticizers
Exposures	Glucose/hypertonic solutions
β-blockers	
Talc	
Asbestos	
Intraperitoneal chemotherapy	
Abdominal lavage disinfectants	
Gastrointestinal diseases	
Hepatic ascites	
Intraabdominal malignancies	
Diseases of reproductive organs	
Luteinizing thecoma of the ovary	
Endometriosis	
Ventriculoperitoneal shunt	

(From Y. Kawaguchi, H. Kawanishi, S. Mujais, et al., Encapsulating peritoneal sclerosis: definition, etiology, diagnosis, and treatment. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis, Perit. Dial. Int. 20 [Suppl. 4] [2000] S43–S55.)

ENCAPSULATING PERITONEAL SCLEROSIS

Encapsulating peritoneal sclerosis (EPS) is recognized as being the most serious and feared noninfectious complication of peritoneal dialysis. Historically, this condition has also been known as "sclerosing peritonitis," "sclerosing encapsulating peritonitis," and "abdominal cocooning." The first case in PD patients was reported in 1980 by Gandhi.[119] Since then, our knowledge of this rare condition has improved considerably.

Definition and Epidemiology

EPS has been defined by the International Society of Peritoneal Dialysis as "a clinical syndrome continuously, intermittently, or repeatedly presenting with symptoms of intestinal obstruction due to adhesions of a diffusely thickened peritoneum."[120]

Its incidence in PD patients currently ranges from 0.5% to 2.8%.[121–125] This may be a decrease from the late 1980s where incident rates were reported to be as high as 5%-7%.[126] It has been proposed that the use of "biocompatible" PD solutions and improvements in peritonitis rates have accounted for this decrease. While the overall incidence of EPS in PD patients is low, the mortality associated with this condition remains extremely high. Mortality rates among PD patients with EPS have been reported to range between 38%-83%.[121–125] Furthermore, a large Japanese study has recently described a direct relationship between mortality, PD duration and incidence of EPS. Specifically, they noted a 17.2% incidence of EPS and a 100% mortality rate in patients who were on PD for greater than 15 years, versus a 2.1% incidence and 8.3% mortality rate in those on PD for less than 5 years.[121]

A geographic predilection for EPS has also been reported. Not surprising, Japan has the highest incidence of EPS among its PD population, whereas North America has the lowest.[122,125,127] The limited availability of kidney transplantation in Japan making lifelong dialysis a necessity has been cited as the main reason explaining this trend.

Risk Factors

A number of risk factors are associated with the development of EPS in PD patients. These can be classified as PD-related and non-PD related (Table 31-5). Common to all these factors is that they disrupt normal peritoneal membrane physiology and so contribute to membrane damage. While there are many PD-related risk factors associated with EPS, three seem to be the most important: duration of PD, persistent or frequent episodes of peritonitis, and cessation of peritoneal dialysis.

The duration of PD is believed to be the most significant risk factor for EPS. As previously mentioned, Japanese and Australian studies have demonstrated progressive increases in EPS incidence after 8 years on PD.[121,128] It has been speculated that this relationship may be a consequence of the cumulative exposure of the peritoneum to nonphysiological PD solutions, leading to progressive membrane damage.

Compounding the damage from these solutions, persistent or recurring episodes of peritonitis have also been considered strong risk factors for EPS development. From a pathophysiological point of view, peritonitis superimposes a large inflammatory response on an already damaged peritoneal membrane leading to further deterioration. This is especially the case for peritonitis episodes caused by Staphylococcus aureus, fungal organisms and Pseudomonas.[120] In fact, a large Japanese study has recently reported that PD patients who developed EPS had peritonitis rates three times greater than their non-EPS counterparts.[124] Some investigators have questioned the significance of peritonitis in the development of EPS. Their skepticism is grounded in

epidemiological studies demonstrating that EPS is well-documented in patients who have never had an episode of peritonitis.[121,123] Nevertheless, the sheer complexity of EPS development makes it difficult to discount the contribution of peritonitis based on this observation alone.

Recently, it has been observed that PD patients are developing EPS at increasing rates upon discontinuation of PD.[129] This was demonstrated by Kawanishi and colleagues[121] who reported that 93% (37/40) of patients developed EPS upon withdrawal from PD for various reasons. Moreover, it was also noted that the onset of EPS was quite abrupt, occurring within four months of discontinuation. It is tempting to speculate that the withdrawal of PD abrogates the continued removal of cytokines, growth factors, and fibrin from the peritoneal cavity by dialysate. Consequently, these lingering humoral factors propagate ongoing inflammation ultimately leading to the development of EPS.

Another important PD-related risk factor is membrane transport status. Patients who developed EPS have been reported to have higher dialysate to plasma creatinine ratios (D/P Cr), signifying high transport status, earlier in the course of their PD than those who did not.[130] The early onset of rapid transport status may aid in the exudation of cytokines and other growth factors, thereby promoting damage to the peritoneal membrane.

Other PD-related risk factors such as acetate-based dialysis solutions, chlorhexidine disinfectants, plasticizers, and beta-blockers have all previously been implicated in the development of EPS.[131–136] However, despite their almost complete elimination in PD patients, the incidence of EPS has not diminished markedly, making their relative contribution to EPS progression appear to be of lesser importance.

Pathophysiology

In PD patients, morphological changes occur in the peritoneal membrane over time. These changes include the loss of mesothelium, expansion of the compact zone (acellular collagen layer and collagen fibroblast layer), and the development of a prominent vasculopathy.[137] Collectively, this process is called "peritoneal sclerosis" and is the result of ongoing damage to the peritoneum from a variety of factors.[138]

It is important to realize that "peritoneal sclerosis" is not EPS. Rather, it is considered by some to be an early change that may or may not be a step in the evolution of the peritoneal membrane towards EPS. While both conditions share many morphological features, recent studies of patients affected by EPS have demonstrated unique membrane changes. Specifically, positive fibrin staining and a thick degenerative compact zone layer are features not seen in peritoneal sclerosis.[139]

Morphological studies of peritoneal membranes with EPS have guided the development of theories concerning the pathogenesis of this condition. While many of these theories are contradictory, they are all based on the premise that the development of EPS can be stratified into two clinically distinguishable stages: the initial stage, which is characterized by a marked inflammatory state; and the late stage, which is distinguished by the resolution of inflammation and the appearance of peritoneal membrane fibrosis.

The two most plausible theories describing EPS development are in fact complementary. The first, Kawanishi's "Two-Hit" Hypothesis, attempts to explain the pathogenesis of EPS, while the second, Nakayama's "Plasma Leak-to-Response" Hypothesis speculates on the mechanism underlying the membranes' morphological changes.[137,140]

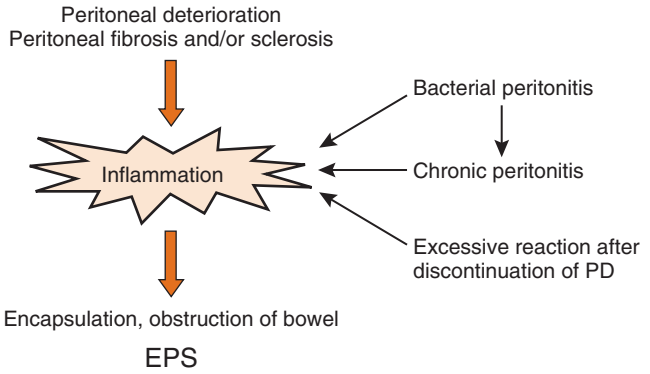


FIGURE 31-5 The "two-hit" hypothesis of encapsulating peritoneal sclerosis. Two factors are required for the onset of EPS: a predisposing factor (first hit), such as peritoneal deterioration from persistent injury caused by bioincompatible peritoneal dialysis solutions, and the initiating factor (second hit), such as infection superimposed on the injured peritoneum. (Adapted from H. Kawanishi, Surgical treatment for encapsulating peritoneal sclerosis, Adv. Perit. Dial. 18 [2002] 139–143.)

1. The "Two-Hit" Hypothesis The "Two Hit" Hypothesis is based on the principle that two events or insults are required for the development of EPS (Figure 31-5). The first "hit" leads to peritoneal deterioration both in structure and function. It is the consequence of ongoing injury to the peritoneal membrane from a variety of factors. Historically, the best described factor is the use of bioincompatible dialysis solutions.[141] It has been well-established that the ongoing exposure of the peritoneum to high levels of glucose, glucose degradation products from heat sterilization, and an acidic pH is associated with morphological changes in the membrane.[136,142] Specifically, the mesothelial cells are preferentially targeted by this "toxic" milieu and undergo marked changes. These changes ultimately lead to the loss of mesothelium on the surface of the peritoneum and alterations in the peritoneal vasculature, which collectively lead to further damage to the peritoneal membrane.[138] Recently, the role of advanced glycation end-products (AGEs) has been implicated in the development of peritoneal damage.[143,144] The binding of AGEs to their receptors (RAGE) on mesothelial and other cells leads to the upregulation and secretion of a variety of humoral factors involved in peritoneal damage.[143,145] Other factors such as plasticizers from the PD catheter, recurrent episodes of peritonitis, and various medications such as chlorhexidine have also been implicated in contributing to peritoneal membrane deterioration.[132,134–136]

Histologically, the damaged peritoneal membrane is characterized by "peritoneal sclerosis."[138] As previously mentioned, it is considered to be a precursor lesion, which requires a second "hit" to trigger the development of EPS. The second "hit" is often facilitated by factors that cause a marked inflammatory response in the peritoneum. This triggers a cascade of events ending with fibrosis, encapsulation of the peritoneum and intestinal obstruction. Historically, two of the most important factors have been acute and chronic bacterial peritonitis episodes, and the discontinuation of PD.[129,146]

Proponents of the "two-hit theory" believe that an additive relationship exists between the degree of peritoneal damage

(first "hit") and the intensity of the inflammatory response (second "hit").[138] In this regard, EPS will develop if the combined intensity of the first and second "hits" crosses a certain threshold. Given that the extent of peritoneal damage increases with the duration of PD, as there is greater exposure of the membrane to priming injurious factors, the degree of the inflammatory stimulus required for EPS onsets need not be as strong over time. This explains why in long-term PD, EPS may develop with a relatively mild inciting event.

2. The Plasma Leak-to-Response Hypothesis While the "two-hit hypothesis" provides a pathogenic model for EPS development, the Plasma Leak-to-Response hypothesis offers insight into this process at the cellular level. This hypothesis proposes that the development of EPS is initiated by vascular alterations in the peritoneum. It is the peritoneal membranes' response to these vascular changes that propagates further damage, ultimately resulting in encapsulation. In the Plasma Leak-to-Response model, EPS development occurs in three stages (Figure 31-6):

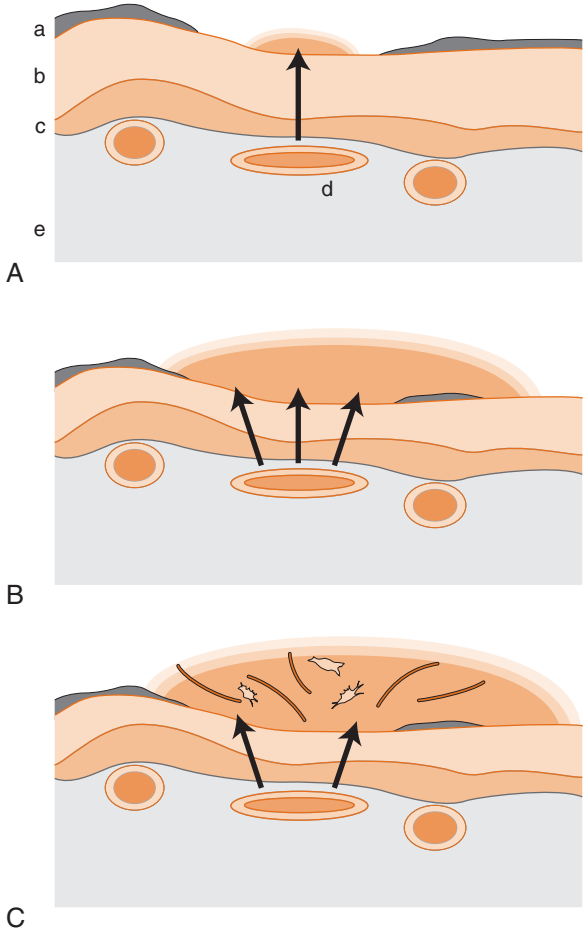


FIGURE 31-6 The "plasma leak-to-response" hypothesis. **A,** Step 1: Increased solute transport in the high transporter membrane state; *(a)* Mesothelium, *(b)* Degenerative layer, *(c)* Proliferative layer, *(d)* Altered vasculature, and *(e)* Adipose tissue. **B,** Step 2: Enhanced plasma leak and accumulation of plasma components over the peritoneal surfaces. **C,** Step 3: Cellular components, including fibroblasts and endothelial precursors, migrate into the plasma and fibrin gel to form a de novo biomembrane. (Adapted from M. Nakayama, The plasma leak-to-response hypothesis: a working hypothesis on the pathogenesis of encapsulating peritoneal sclerosis after longterm peritoneal dialysis treatment, Perit. Dial. Int. 25 [Suppl. 4] [2005] S71-S76.)

Stage 1: Increased Solute Transport As previously stated, ongoing injury to the peritoneal mesothelial cells, imparted by bioincompatible PD solutions, and advanced glycation products (AGEs), leads to changes in the structure and function of these cells. The injured mesothelial cells secrete various cytokines, such as interleukin-6 (IL-6) and growth factors, including vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) that induce angiogenesis of the peritoneal membrane.[147–150] The increased density of peritoneal membrane microvasculature begets increased transport of small solutes across the peritoneal membrane. This is because solute transport occurs at the level of the microvasculature and therefore is proportional to the degree of membrane vascularity.[151] It is believed that this event initiates the inflammatory phase of EPS. Clinically, this stage presents with only ascites. PET testing demonstrates a high transport status, with an increased dialysate to plasma ratio of creatinine (D/P Cr).[152]

Stage 2: Enhanced Plasma Leak and Accumulation of Plasma Components over the Peritoneal Surface This stage is characterized by massive exudation of fibrinogen rich plasma into damaged areas of the peritoneal membrane. Facilitating this enhanced leakage of plasma is the altered peritoneal vasculature formed in Stage 1. The exuded plasma is rich in fibrinogen, cytokines, and other growth factors. It spreads out over the native peritoneal surface depositing the various inflammatory factors as it goes. This creates a marked inflammatory state that is ripe for the formation of a de novo membrane. The clinical hallmarks of this stage include an increase in inflammatory markers such as C-reactive protein (CRP), nonspecific gastrointestinal symptoms, and bloody effluent.

Stage 3: Cellular Migration into the Fibrin Gel, Leading to the Formation of Biomembrane The cytokines and growth factors deposited on the peritoneal surface recruit macrophages and fibroblasts that lay down collagen, fibrin, and blood vessels on the surface of the native peritoneal membrane forming a new membrane. In turn, the newly formed vasculature, which itself is leaky, further increases plasma extravasation, leading to amplification of the entire process.

At some point, the extensive fibrin-collagen network that was laid down leads to the cessation of further plasma leakage and capsule formation ensues. With this change, the inflammatory phase of EPS ceases and the fibrotic state begins. This stage manifests clinically with signs and symptoms of ileus and bowel obstruction.

A proposed pathogenetic model of EPS based on animal studies has recently been published (Figure 31-7).[153] It combines features of Kawanishi's Two-Hit Hypothesis and the Plasma Leak-to-Response Hypothesis. Briefly, it proposes that long-term exposure to PD causes defective peritoneal regeneration and mesothelial cell denudation. This stimulates fibroblast activation leading to fibrosis, angiogenesis, and vasculopathy. Additionally, defective fibrolysis contributes to increased fibrin deposition in peritoneal tissue, leading to progressive peritoneal thickening and fibrosis. Inflammatory stimuli from peritonitis act as a second hit, causing further mesothelial damage, recruitment of inflammatory cells, and eventually progressive fibrosis and adhesions.

Interestingly, while biologically plausible, animal models of EPS are too simplistic because they fail to account for

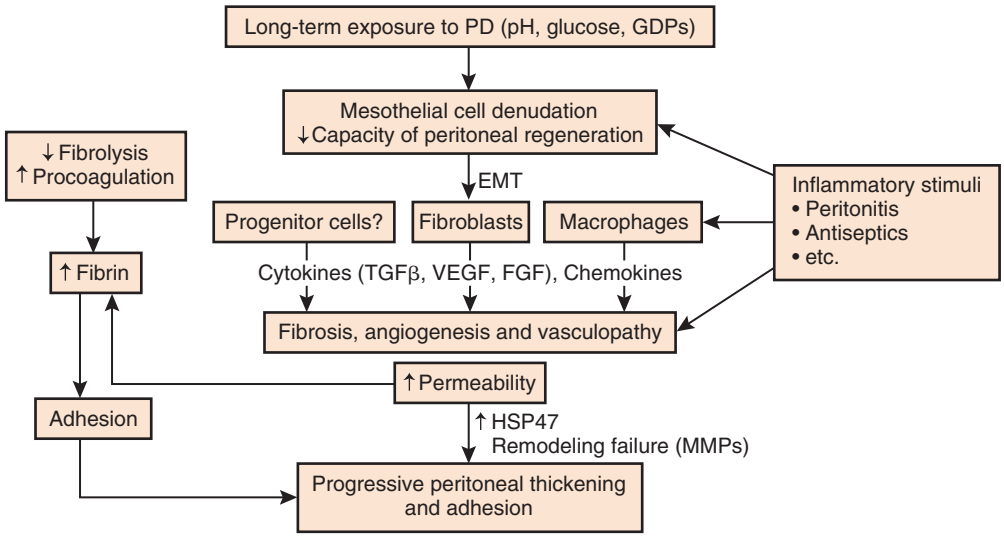


FIGURE 31-7 Proposed pathogenesis of encapsulating peritoneal sclerosis. Long-term PD causes defective peritoneal regeneration with mesothelial cell denudation. Increased numbers of activated fibroblasts yield fibrosis, angiogenesis, and inflammation and additional failure of remodeling of fibrotic tissue lead to progressive fibrosis. Defective fibrinolysis by mesothelial cells increased fibrin deposition in the peritoneal tissue, contributing to progressive peritoneal thickening and adhesion. Inflammatory stimuli act as a second hit, which causes further mesothelial damage, recruitment of inflammatory cells, and eventually progressive fibrosis and adhesion. (Adapted from S.H. Park, Y.L. Kim, B. Lindholm, Experimental encapsulating peritoneal sclerosis models: pathogenesis and treatment, Perit. Dial. Int. 28 [S5] [2008] S21–S28.)

genetic factors in EPS development. Undoubtedly future models will have to incorporate the role of genetics in EPS. Animal studies have demonstrated that polymorphisms in genes expressing various inflammatory cytokines such as IL-6 affect small solute transport across the peritoneal membrane.[154] This is mediated primarily through an inflammatory response initiated by increased expression of these cytokines, which in turn initiates a cascade of events ultimately leading to membrane damage. Based on these studies, it is tempting to speculate that perhaps PD patients who develop EPS have polymorphisms in certain genes expressing inflammatory cytokines, angiogenic factors, and fibrotic factors. Further study into the function of various genetic polymorphisms will likely improve our ability to identify which PD patients are at risk for EPS.

Clinical Presentation and Diagnosis

EPS is a slowly progressive disorder that may remain asymptomatic for a prolonged period of time. When symptoms and signs do arise, they are often vague and nonspecific; therefore, a high index of suspicion of EPS is required.[125] Abdominal pain, nausea, vomiting, changes in bowel habits, and fever are often the initial manifestations of EPS. As peritoneal sclerosis progresses and gastrointestinal function further declines, these symptoms increase in frequency and intensity. Soon anorexia sets in, leading to weight loss and malnutrition. Other important clinical signs indicating peritoneal damage may also be present such as a hemorrhagic effluent, recurrent episodes of "culture negative" peritonitis, and problems with ultrafiltration. Ultimately, frequent episodes of bowel obstruction occur, which clinically herald a state of peritoneal fibrosis.

Biochemically, EPS may present with aberrations in laboratory findings consistent with systemic inflammation. These include elevated levels of CRP, refractory anemia, and hypoalbuminemia.[129]

Given the large variability in the presentation of EPS, the clinical picture alone is insufficient to diagnose this condition, and further testing is usually warranted. Historically, radiological evaluation of the peritoneum and its structures has been the first step in confirming the diagnosis of EPS and in ruling out other conditions. There are four radiological findings that are pertinent to confirmation of the diagnosis of EPS: 1) peritoneal thickening and encapsulation, 2) intestinal obstruction, 3) peritoneal calcification, and 4) cocooning.[120] These findings can be quite variable in a given patient depending on the radiological modality chosen and the stage of EPS.

Plain abdominal films have demonstrated limited utility in diagnosing EPS. While x-rays may detect dilated small-bowel loops, air-fluid levels, and peritoneal calcification, they possess limited specificity.[155]

On the other hand, abdominal ultrasound is an excellent modality for detecting changes associated with EPS. It can demonstrate multiple abnormalities in the peritoneal cavity including the characteristic trilaminar appearance of the bowel wall.[156,157] One of the drawbacks of this modality is it requires the presence of fluid in the peritoneum for optimal sensitivity and is operator dependent.

CT is the most sensitive and specific modality for demonstrating findings characteristic for EPS.[157–159] Some of these findings can be subtle and therefore subject to interpretation by the reviewing radiologist. This may be the reason for the "overcalling" of EPS based on CT findings. In an attempt to abrogate such variability, a recent study has demonstrated that in the correct clinical setting, the diagnosis of EPS can be made if bowel tethering and peritoneal calcification are found on CT study.[160] Despite CT scanning being a valuable tool in the diagnosis of EPS, it has been found to be not very useful as a screening tool.[160] Specifically, in a retrospective study of 13 EPS patients with CT scans 4 months before their diagnosis, this modality was unable to detect any abnormal findings

in nine patients.[160] This may attest to the notion that EPS may have a fulminant course and early detection through screening may be unwarranted. Obviously, further study is needed to confirm this observation. The role of MRI in diagnosing EPS is still being evaluated; however, preliminary data suggest results similar to CT.[161,162]

Other noninvasive methods for detecting EPS include the utilization of novel biomarkers found in the PD effluent. Examples include cytokines such as IL-6 and transforming growth factor beta (TGFβ); gelatinases such as metalloproteinase-2 (MMP-2); and angiogenic factors including VEGF and fibrin degradation products.[163–165] As previously mentioned, these factors are upregulated in response to peritoneal inflammation and drain into the peritoneal cavity where they can be assayed in the PD effluent. Despite the positive correlation between levels of these markers and the amount of peritoneal inflammation, none have demonstrated efficacy in detecting EPS or its precursor lesion.[163–165] Based on this, their routine use is not warranted.

The gold standard for diagnosing EPS remains direct visualization of the peritoneal membrane. At times, histological examination may be required; however, the diagnosis of EPS is essentially confirmed when gross examination of the peritoneal cavity demonstrates thickening of the peritoneum, encasing some or all of the intestines in a tanned, leathery cocoon.[133]

Pathologically, EPS is characterized by complete loss of the mesothelium, accompanied by gross interstitial thickening within the membrane. The thickened interstitial layer is composed of fibroblasts, collagen, abnormal vasculature, and at times inflammatory mononuclear cells.[138,166] Marked fibrin staining is also found along the membrane indicating extensive fibrin deposition.[138,166]

Therapeutic Approaches in Encapsulating Peritoneal Sclerosis

The relative paucity of EPS cases impart substantial difficulty when attempting to study therapeutic interventions. In fact, most studies focusing on EPS therapy are small, anecdotal, or observational accounts, which limit the generalizability of the results.[129,167–177] Since the original reports of EPS were published, the management of this condition has evolved. While surgical management was the mainstay of treatment in the past, insights into the pathophysiology of EPS have permitted the introduction of novel medical therapies. Despite being unable to demonstrate a substantial change in the natural history of EPS on a consistent basis, these therapies have helped reinforce the notion that early initiation of treatment is paramount to potentially facilitate some degree of improvement. In this regard, a staging classification of EPS has recently been proposed by Kawanishi and colleagues.[178,179] It stratifies EPS into four stages based on clinical and pathological findings at different times in the course of EPS development. This allows for rational therapeutic interventions to be used according to the stage of EPS (Table 31-6).

1. Conservative Measures As previously mentioned, gastrointestinal (GI) symptoms are pervasive in EPS. As a result, patients often decrease their oral intake substantially. In addition, patients are frequently highly catabolic. Both factors ultimately lead to malnutrition, which plays an important role in the morbidity and mortality associated with this condition.

TABLE 31-6 Proposed Staging of Encapsulating Peritoneal Sclerosis

STAGE	CLINICAL FINDINGS	THERAPEUTIC APPROACH
Stage 1 (pre-EPS period)	Loss of ultrafiltraction capacity Development of a high transport state Hypoproteinemia Bloody dialysate, ascites Calcification of peritoneum	Peritoneal rest Peritoneal lavage Glucocorticoids
Stage 2 (inflammation period)	Increase in C-reactive protein Increase in white blood cells Fever Bloody dialysate Ascites Weight loss Appetite loss Diarrhea	Glucocorticoids
Stage 3 (encapsulating or progressive period)	Disappearance of the signs of inflammation Appearance of symptoms/signs of ileus (nausea, vomiting, abdominal pain, constipation, abdominal mass, ascites)	Glucocorticoids Total parenteral nutrition Tamoxifen
Stage 4 (ileus or complete period)	Anorexia Complete ileus Abdominal mass	Surgical intervention

(From H. Nakamoto, Encapsulating peritoneal sclerosis—a clinician's approach to diagnosis and medical treatment, Perit. Dial. Int. 25 [Suppl. 4] [2005] S30–S38.)

In mild cases of EPS, where the GI side effects are tolerable, nutritional support through NG feeds or high caloric beverages combined with antiemetics should be instituted. This is in contrast to more severe cases, particularly ones with obstruction, where parenteral feeding and bowel rest may be necessary. While one small study demonstrated a 51% recovery rate in patients treated with only TPN and transfer to hemodialysis, other reports demonstrate substantially worse outcomes.[121,122,179] This disparity may be due to complications related to use of TPN itself, but more importantly, it may relate to the cessation of PD, which may accelerate progression of EPS. Given the small numbers of patients in these studies, it is difficult to fully elucidate the contribution or lack thereof of TPN. It should also be remembered that these patients are at risk for refeeding syndrome and so should be followed closely.

2. Corticosteroids Corticosteroids have become paramount in the treatment of EPS, with some studies documenting response rates as high as 100%.[167] While this rate was demonstrated in a small study, the largest study to date involved 39 patients and showed a 38.5% rate of recovery.[121] Invariably, most patients who have responded to corticosteroid therapy were on PD for shorter duration than their counterparts who did not respond. This indicates that timing of steroid initiation is important. Ideally, steroid therapy should commence in the early stages (pre-EPS/inflammatory period) of EPS. Failure to do so may lead to an inability to prevent fibrosis and capsule formation and the full-blown manifestations of EPS. This has been suggested by animal models, where the early initiation of steroid therapy minimized the progression to EPS.[168]

While there is consensus for early steroid initiation, there is no marker to indicate optimal timing. Furthermore, it is

unclear what is the best dosing regimen, that is, pulse or continuous corticosteroid. In the past, markers of inflammation such as CRP, ferritin, and hypoalbuminemia have been used to guide clinical decision-making; however, these markers are neither sensitive nor specific for EPS. Both low-dose steroids and pulse steroid regimens, followed by maintenance therapy, have been used successfully.[121]

Ultimately, clinical judgment must be used to decide when to initiate this therapy and at what dose. In this regard a trial of corticosteroids should be administered fairly quickly in most patients who fail to respond to more conservative therapies after peritonitis or other intraabdominal infection has been ruled out.

3. Tamoxifen Tamoxifen is a nonsteroidal, anti estrogenic drug that has become ubiquitous in the management of breast cancer. It has also demonstrated efficacy in the treatment of various fibrotic diseases and therefore has garnered interest as a therapeutic agent for EPS.[169] While its role in attenuating the effects of EPS is unclear at present, insights have been gained into its potential mechanism of action through various animal models. Tamoxifen upregulates the production of TGFβ1, a cytokine, which in turn stimulates MMP9.[169] MMP-9 degrades type IV collagen, an extracellular matrix component that injures mesothelial cells, and so abrogates the epithelial-to-mesenchymal transformation of mesothelial cells.[180] By helping maintain the phenotypic integrity of mesothelial cells, tamoxifen may play a role in the preservation of the peritoneal membrane.

Tamoxifen is an attractive therapy for EPS because it is devoid of the catabolic and immunosuppressive effects of corticosteroids. However, it does possess serious side effects most notably increased thromboembolic risk. To date, the literature regarding the use of Tamoxifen in EPS is sparse, including four case reports and a case series of four patients.[169–173,181] While all the reported EPS patients treated with tamoxifen demonstrated either recovery from EPS or prevention of its development, it is difficult because of a number of methodological issues to draw conclusions regarding its role. These include the small number of patients treated, concomitant steroid use, and variability in treatment duration. Obviously, further study into the role of tamoxifen in the management of EPS is warranted.

4. Surgical Management Despite the use of TPN, steroids, and recently tamoxifen in the management of EPS, approximately 50% of patients do not respond and eventually require surgery.[174] The Japanese have a wealth of experience in the surgical management of EPS and have demonstrated that in experienced hands, surgery can improve symptoms and survival.

The current surgical technique used for EPS involves the lysis of intestinal adhesions by a sharp instrument, a process known as enterolysis.[174] The goal is to remove the fibrotic tissue. Numerous studies have proven this technique to be quite safe and effective. In a prospective Japanese study of 27 patients with EPS, 20 of whom received preoperative steroids, Kawanishi showed complete resolution of ileus symptoms in 22 patients.[182] The mortality rate was 4%, which is a dramatic improvement from previous surgical interventions. Subsequent studies, albeit smaller in size, had similar results.[183]

Surgical intervention should be sought before the appearance of malnutrition, which may increase postoperative morbidity and mortality. There are four accepted indications for surgery in EPS: persistent bowel obstruction, failing nutritional status, failure to respond to conventional therapy, and recurrent episodes of peritonitis secondary to bowel compromise.[184] Surgery should be performed by a dedicated surgeon familiar with the management of EPS.

While surgery reverses intestinal obstruction, it fails to abrogate peritoneal deterioration, leading to recurrence of EPS in most patients, usually within 6 to 12 months.[183] Interestingly, it has been demonstrated that in recurrent cases there is an increase in peritoneal microvessels.[185] This propagates leakage of fibrin onto the damaged mesothelium, leading to encapsulation.

5. Immunotherapy and Other Experimental Agents There are reports in the literature of immunosuppressants being used to treat EPS.[175–177] Agents such as azathioprine or mycophenolate mofetil (MMF) combined with prednisolone have been used in the past and have demonstrated some efficacy.[175,176] While the results are promising, the number of cases is small and confounded by concurrent steroid use, which limits the interpretation of these studies. Other novel therapies including blockers of the renin-angiotensin system (RAS), VEGF inhibitors, everolimus, hepatic growth factor (HGF) inhibitors, colchicine, and gene therapy have demonstrated benefit in animal models.[186–189] Further evaluation of these agents is necessary to draw definite conclusions.

Prevention of Encapsulating Peritoneal Sclerosis

Despite recent advances in determining the pathogenesis of EPS, preventing this condition continues to be extremely difficult. Thus far, the most logical approach to prevent EPS is to implement practices that address risk factors. In this regard, such practices include: 1) effective peritonitis prevention strategies, 2) early and aggressive management of peritonitis, and 3) PD catheter removal in nonresolving peritonitis. Although it is unclear whether the introduction of these practices is efficacious, they are relatively safe, simple, and inexpensive to initiate. Therefore, there is little risk in initiating them.

Similarly, more controversial practices aimed at mitigating the development of EPS have also been attempted with equivocal results. These practices include the preemptive discontinuation of PD, peritoneal lavage upon cessation of PD, and the use of novel antifibrotic medications.[121,128,190–192]

As previously mentioned, time on PD is a risk factor for EPS. However, the practice of preemptive discontinuation of PD with transfer to hemodialysis (HD) has not demonstrated any merit in a prospective study.[121] In fact, this practice may unintentionally act as a stimulus for the development of EPS. It has been recommended that preemptive transfer to HD only be considered in patients with a very high risk for EPS.[184] These patients usually possess many of the risk factors previously discussed. The effect of this management strategy is currently unknown. Obviously close follow-up would be warranted as EPS can develop many years after discontinuation of PD.

Another early intervention aimed at preventing EPS with cessation of PD is peritoneal lavage. It has been proposed as a therapy to remove accumulated fibrin, which is a key player in capsule formation. While one small study demonstrated improvement in transport state after 6 months of daily lavage, subsequent studies have failed to confirm this trend.[190,191]

In fact, in these studies, EPS developed in 50% and 52% of patients undergoing lavage.[190,191] Because of this, peritoneal lavage has been abandoned as a prophylactic measure.

EPS AND RENAL TRANSPLANTATION

There has been much speculation about the role transplantation plays in the development of EPS after a report from 2 Dutch units demonstrated an increase in the number of cases of EPS occurring after renal transplantation.[193,194] These cases presented with an acute onset of EPS that was characterized by severe symptoms of obstruction, which is in contrast to the typical presentation of EPS. Further work by deFrietas and colleagues[195] reported 23 cases of EPS occurring within 1 year after renal transplant in patients previously on PD.

To explain the phenomenon of posttransplant EPS, both termination of PD and transplantation-related factors can be invoked.[121,196–198] As mentioned previously, the discontinuation of PD leads to an increase in concentrations of fibrin and proinflammatory mediators, which can give rise to and propagate EPS. Certain immunosuppressant medications have been implicated in the pathogenesis of EPS.[199] This is especially the case for profibrotic agents such as calcineurin inhibitors, which may enhance the inflammatory fibrotic processes already initiated in the visceral peritoneum.[200] Using rat models, it has been demonstrated that the addition of cyclosporine (CSA) in conjunction with ongoing PD leads to angiogenesis and increased peritoneal fibrosis.[200] Moreover, the trend towards use of corticosteroid withdrawal protocols in newer immunosuppressive regimens may reveal an inherent tendency to develop EPS posttransplantation. By withdrawing steroids, the inflammatory response can propagate unabated, leading to the progression of EPS. This has been noted in a case report of EPS developing after steroid tapering in a transplant patient.[198] Increase in steroid dose lead to a regression of EPS.

The approach to the diagnosis and management of EPS post transplantation is similar to that of the nontransplant population. However, the differential diagnosis must include transplant related causes of gastrointestinal disturbances including MMF induced GI dysmotility, lymphomas, and various infections. Consideration could be given to changing a calcineurin inhibitor to sirolimus.

A full list of references are available at www.expertconsult.com.

Chapter 32

TRANSPLANTATION IMMUNOBIOLOGY

Nader Najafian, M.D., and Mohamed H. Sayegh, M.D.

When an organ or tissue from one member of a species is transplanted into a nonidentical member of the same species, an immune response ensues. This response is termed the *alloimmune response*, and it is primarily orchestrated by initial T-cell recognition of alloantigens (allorecognition, signal 1). However, full activation of T-cells requires in addition to signal 1 two other sequential signals: signal 2 delivered by ligation of costimulatory receptors on T-cells by ligands on antigen-expressing cells (APC) and signal 3 delivered by multiple cytokines that regulate cell proliferation, differentiation, and survival/death. The first part of this chapter reviews the process of T-cell allorecognition with particular emphasis on recent advances in our understanding of T-cell costimulatory pathways and novel cytokines in regulating different phases of T-cell responses in transplant rejection. Activation of alloreactive T-cells subsequently leads to the initiation of the effector mechanisms of the immune system, resulting in allograft destruction. Recently, B-cells and alloantibodies against human leukocyte antigen (HLA) and non-HLA targets have been increasingly recognized as critical in the pathogenesis of acute and chronic allograft dysfunction. Furthermore, while T-cells alone are necessary and sufficient for the rejection of allografts, evidence is accumulating on the role of humoral and cellular components of the innate immune system in allograft rejection and prevention of tolerance. The second part of this chapter focuses on the various effector mechanisms of allograft rejection. The ultimate goal in clinical transplantation is to induce a state of donor-specific immunological tolerance, where recipients can accept organs without the need of exogenous immunosuppression. The final part of this chapter reviews the most promising approaches to induce transplantation tolerance. In particular, we highlight the biological basis and putative mechanisms of tolerance and discuss some of the major stumbling blocks to the induction and maintenance of tolerance in clinical transplantation.

THE ALLOIMMUNE RESPONSE

A. Transplantation Antigens

Major Histocompatibility Complex

The Major Histocompatibility Complex (MHC) antigens are the strongest transplantation antigens, and they can stimulate a primary immune response without priming. The alloimmune response arises as a direct result of the normal function of MHC molecules. First, the recipient T-cell receptor's recognition of donor MHC/peptide complexes is the central event in the initiation of an alloimmune response. Second, allogeneic donor HLA antigens themselves are the main immunological targets of different effector arms on the immune system. In addition, antibodies against donor HLA antigens due to pregnancies, blood transfusions, or previous transplantation cause hyperacute or accelerated acute graft rejection when they are present before transplantation. Recent data have also implicated their appearance after transplantation and their role in both acute rejection and chronic allograft dysfunction.

T lymphocytes recognize foreign (nonself) antigens in the context of self cell-surface molecules encoded in the MHC.[1] In humans, this genetic region is located in a 3.5 million base-pair region on the short arm of chromosome 6. This locus is further subdivided into three clusters based on the structure and function of the proteins encoded by the genes. Human MHC molecules are called HLAs, and the three regions have been designated HLA class I, class II, and class III (Figure 32-1).

HLA *class I* molecules (classic HLA-A, -B, and -C, and other nonclassic molecules) are composed of a 44-kD heavy chain and a 12-kD light chain (Figure 32-2, *A*).[1,2] The amino terminus portion of the heavy chain that extends into

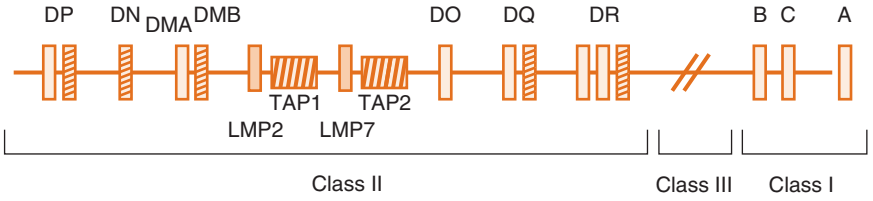


FIGURE 32-1 Genomic organization of the human major histocompatibility complex (MHC). See text for explanation. (From E. Noessner, A.M. Krensky, HLA and antigen presentation, in: N.L. Tilney, T.B. Strom, L.C. Paul [Eds.], Transplantation Biology: Cellular and Molecular Aspects, Lippincott-Raven, New York, 1996, p. 31.1.)

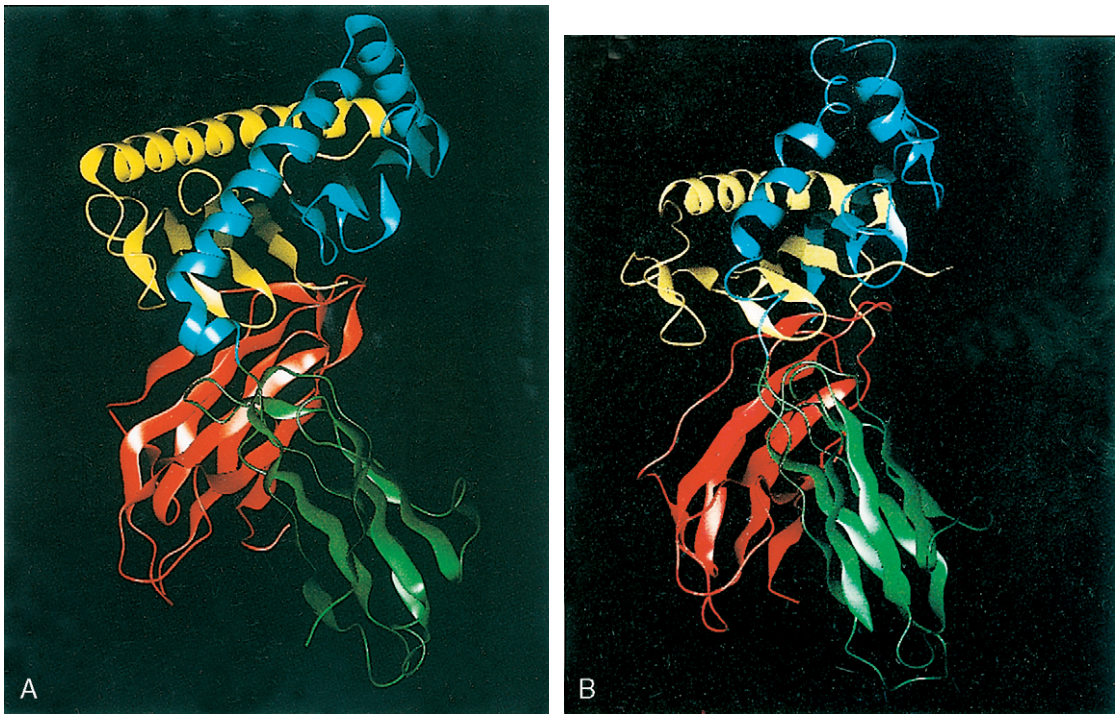


FIGURE 32-2 Computer model of HLA **(A)** class I (HLA-B27) and **(B)** class II (HLA-DR1) structures. The peptide-binding region, made up of two α helices supported by a floor of β strands, is at the top of both views. For HLA-B27, α_1 domain is yellow, α_2 domain is red, β_1 domain is blue, and β_2 domain is green. The colors are the same for homologous domains in the two proteins. (From R.N. Germain, MHC-dependent antigen processing and peptide presentation: providing ligands for T lymphocyte activation, Cell 76 (2) (1994) 287-299.)

the extracellular space is composed of three domains: alpha1, alpha2, and alpha3. The alpha1 and alpha2 domains interact to form the sides of a cleft (or groove). The cleft is the site where foreign proteins bind to MHC molecules for presentation to T-cells. The highly variable amino acid residues located in the groove determine the specificity of peptide binding and T-cell antigen recognition. The light chain, β_2-microglobulin, stabilizes the heavy chain such that displacement of β_2-microglobulin from the class I molecule causes a loss of heavy chain native structure. Class I molecules are expressed on essentially all nucleated cells. The function of intact class I molecules is to present antigenic peptides as protein fragments (peptides) in the context of self to T lymphocytes. HLA class I molecules are highly polymorphic. This polymorphism aids in maximizing the potential for peptide binding by the species. Peptides bind within the HLA class I groove (Figure 32-3, *A*) based on the sequence of amino acids in the peptide-binding region.[3] HLA class I molecules tend to bind peptides of 9 to 11 amino acids in length. These peptides fit tightly into the groove and do not extend out of the ends of the molecule. MHC class I molecules generally present endogenous proteins (Figure 32-4).[4] These proteins, such as viruses and normal self proteins, are degraded in the cytoplasm in proteosomes. Short peptide sequences are then moved to the endoplasmic reticulum through specific transporters associated with antigen presentation (TAP transporters). In the endoplasmic reticulum, these peptides associate with class I heavy chain and β_2-microglobulin, and the mature complex is transported to the cell surface, where it can be recognized by T lymphocytes. Peptides sit in the middle of the groove and run the length of the cleft. The rules for peptide binding are restricted to certain "motifs" based on the polymorphisms described earlier but are lax enough to permit the binding of many different peptides to a single HLA type (allele). Antigens associated with class I molecules are recognized by cytotoxic $CD8^+$ T lymphocytes.

The second major region of the MHC is called the *class II locus* (see Figure 32-1).[1] HLA class II molecules—HLA-DP, DQ, and DR—are composed of polymorphic α and β chains of about 35 and 31 kD, respectively. These two chains associate to form a peptide-binding region, but unlike class I molecules, determinants of the peptide-binding region are contributed by both chains (Figure 32-2, *B*).[2] MHC class II molecules bind longer peptides—typically 12 to 28 amino acids. In contrast to class I, MHC class II molecules have binding grooves that are open at the ends, permitting peptides of greater lengths to extend beyond the groove

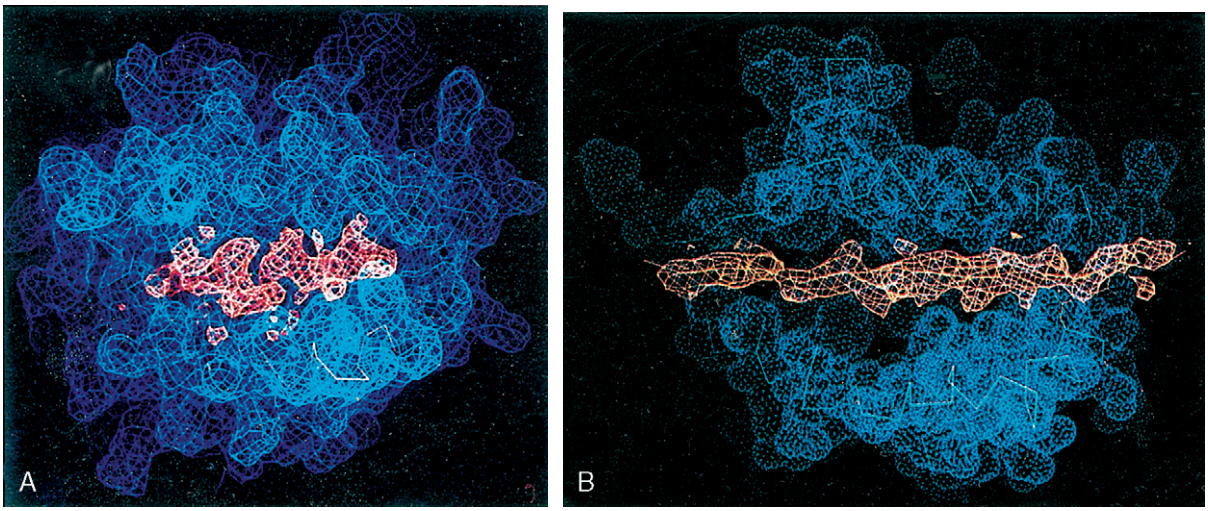


FIGURE 32-3 Peptide binding to HLA class I (HLA-A2) **(A)** and class II (HLA-DR1) **(B).** The view is looking down on the molecule as a T lymphocyte might "see" it. The two α helices forming the rim of the peptide binding site are blue, and electron densities corresponding to bound peptides are shown in red. (**A** from P.J. Bjorkman, M.A. Saper, B. Samraoui, W.S. Bennett, J.L. Strominger, D.C. Wiley, Structure of the human class I histocompatibility antigen, HLA-A2, Nature 329 (6139) (1987) 506-512; **B** from J.H. Brown, T.S. Jardetzky, J.C. Gorga, et al., Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1, Nature (364) (1994) 35.)

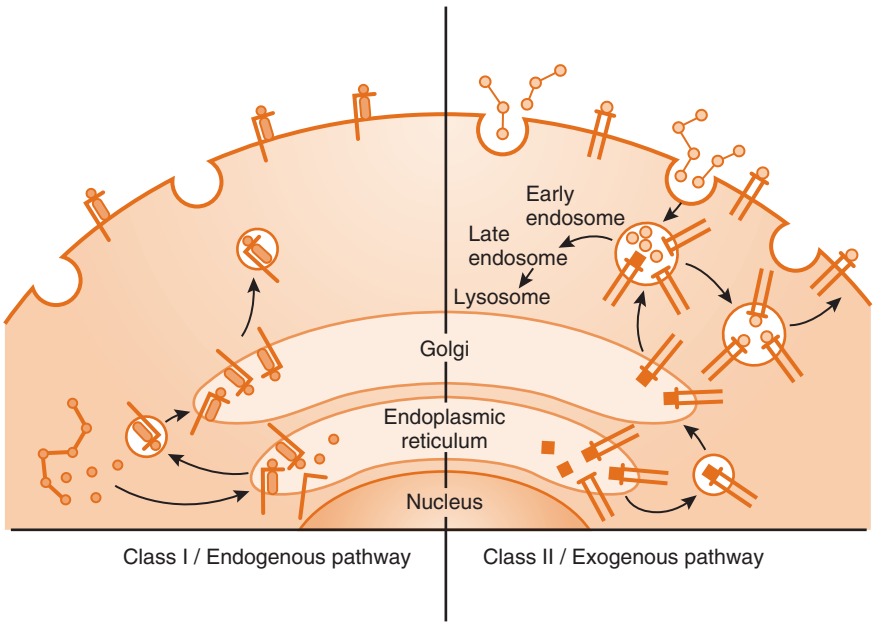


FIGURE 32-4 Antigen processing and presentation. In the endogenous pathway *(left)*, HLA class I molecules bind to peptides from endogenous antigens. The proteosome breaks up cytoplasmic proteins into peptides that enter the endoplasmic reticulum via specific transporters. In the endoplasmic reticulum, peptides associate with HLA class I molecules and from the mature complex that is exported through the Golgi apparatus to the plasma membrane. The exogenous pathway *(right)*, HLA class II molecules bind peptides from exogenous antigens. Exogenous proteins enter the cell by endocytosis and are degraded to peptides in endosomes and lysosomes. Class II molecules bind peptides in the "compartment for peptide loading" and are transported to the plasma membrane. (From A.M. Krensky, Transplantation immunobiology, in: R. Jamison, R. Wilkinson (Eds.), Nephrology, Chapman and Hall, London, 1997, p. 1051. Reprinted by permission of Hodder Arnold.)

(see Figure 32-3, *B*).[5] Class II molecules tend to bind antigens that are derived from the exogenous pathway (see Figure 32-4). MHC class II α and β chains associate in the endoplasmic reticulum with an invariant chain, a portion of which binds in the antigen-binding groove. This invariant chain appears to both protect the groove from peptide binding and permit proper folding of the class II complex. A nonameric form exits the endoplasmic reticulum and moves through the Golgi apparatus and into an endosomal compartment. Within the endosome, the invariant chain is degraded, leaving a shorter class II–associated invariant chain peptide (CLIP) fragment in the groove. Peptides from the extracellular space are taken up into endosomes by endocytosis and targeted to the "compartment for peptide loading." Within this specialized intercellular compartment, exogenous peptides displace CLIP, and the mature heterotrimeric complex (α, β, and peptide) is transported to the cell surface, where it can be recognized by T lymphocytes. Class II molecules are expressed only on professional APCs, and antigens bound to class II MHC molecules are usually recognized by $CD4^+$ helper T-cells. In addition to the classic class II antigens, the MHC class II region encodes proteins that make up the proteasome (low-molecular-weight proteins LMP-2 and LMP-7) and the TAP transporters (TAP-1 and TAP-2) (see Figure 32-1). Polymorphisms associated with these structures probably also contribute to the specificity and diversity of peptide binding and antigen presentation. The class III region encodes a variety of proteins of immunological relevance (see Figure 32-1). These include the tumor necrosis factor (TNF) and the complement proteins factor B and C4.

As just outlined, MHC molecules are highly polymorphic, as each MHC locus can express any one of hundreds of different molecules encoded by various *alleles*. The set of different alleles expressed on one chromosome is called a haplotype. Each parental chromosome 6 provides a haplotype to the offspring. Haplotypes are usually inherited intact from each parent, although crossover between the A and B locus occurs in about 2% of offspring, resulting in a recombination and a new haplotype. A genotype is the sum of two haplotypes. A child is by definition a one-haplotype match to each parent unless recombination has occurred. In addition, the MHC molecules are codominantly expressed—that is, an individual expresses alleles from both chromosomes at each locus. Therefore, the MHC genotype of an individual consists of 12 different MHC molecules (two alleles from each of six loci). In clinical transplantation, the most important MHC genes are HLA-A,-B and -DR. The antigenic determinants of their six alleles are the focus of attempts at HLA matching to improve graft survival. Given the remarkable degree of polymorphism exhibited by MHC genes, there are 88 recognized antigens encoded by more than 1000 distinct alleles, and the number of new alleles is still increasing. The HLA antigens were initially identified using antisera obtained from multiparous women and named in the sequence they were discovered (for example, A1, A2, etc.). However, introducing DNA technologies for HLA testing resulted in the identification of growing numbers of alleles that could be identified by their unique nucleotide sequences within the antigen designations. Thus, the serological nomenclature was modified to associate alleles with antigens, and four-digit designations were developed in which antigen designation makes up the first two digits and the sequential allele designation makes up the third and fourth digits. For example, the first allele for HLA-A1 is HLA-A*0101, which includes the locus (A), an asterisk to indicate the typing was performed by DNA methods, the serological antigen (01), and the allele number (01). The correlation between alleles and antigens is updated periodically, more recently in the *HLA Dictionary 2008*, which includes information on 832 new alleles and updated information on 766 previously listed alleles.[6] While HLA gene polymorphism plays a critical role in protective immunity by enabling the binding and presentation of a wide variety of microbial peptides to T-cells, it could potentially create a practical barrier to successful transplantation. In fact, it has recently been shown that differences between MHC molecules by as little as one or two amino acids (called micropolymorphism) in the antigen-binding cleft can change the size and diversity of the peptide repertoire presented by each HLA molecule.[7] It is not feasible to select a completely HLA matched donor for every potential recipient because of the enormous polymorphism of the HLA system. While allele differences between the donor and the recipient of bone marrow transplants (even micropolymorphism) lead to graft-versus-host disease, its significance in clinical kidney transplantation remains to be seen.

The alloimmune response is strong and does not require priming.[8] At least part of the basis for the greater magnitude of the allogeneic response is the relatively high frequency of T-cell precursors that are capable of responding to a foreign MHC antigen. For example, the frequency of specific T-cells to conventional antigens is approximately 1 in 10^4 to 10^5, whereas the frequency responding during allogeneic stimulation can be as high as 1 in 10^1 to 10^2. The concept of positive and negative selection in the thymus (see mechanisms of self tolerance) also helps to explain the strength of the alloimmune response.[9–11] During development, T-cells with receptors of too high an affinity are deleted (negative selection), whereas those with too low an affinity are not selected. The result of this selection is that T-cell receptors (TCRs) of intermediate affinity exit the thymus and enter the periphery. Within an individual, clonal deletion occurs early in development. Potentially, autoreactive clones (with too high an affinity for self) are deleted; failure of deletion of some clones may lead to autoimmunity. In the case of transplantation across an allelic difference, however, the recipient's T-cells do not contact allo-MHC molecules during development in the thymus and thus escape the deletion (negative selection) imposed by interaction with self-MHC. Thus, the result is the large number of donor MHC/peptide complexes on the graft to which a potential recipient has not been tolerized during ontogeny. Moreover, the relatively low affinity of any given TCR for its ligand suggest that each T-cell could potentially recognize more than one MHC/peptide complex.[12] The high density of alloantigens on the surface of an allograft additionally contributes to the strong T-cell response. In addition, because recipient T-cells recognize intact allogeneic MHC molecules directly (see following), they are stimulated maximally by the high density of MHC on the surfaces of transplanted cells.

Minor Transplantation Antigens

Studies involving MHC identical grafts in mice indicate that minor histocompatibility antigens can also mediate rejection. Recipient T-cells can be directly primed to minor histocompatibility antigens. A minor histocompatibility antigen is molecularly defined as a donor-derived peptide presented on a donor cell by an MHC molecule shared by a donor and a recipient. Note that the donor and the recipient express the same MHC molecules. Donor DCs directly prime $CD8^+$ T-cells to become effector cells without the need for further antigen processing by recipient APCs. As one illustration, $CD8^+$ T-cells from female C57BL/6 mice specific for male-derived H-Y Uty peptide + MHC class I mediate rejection of syngeneic C57/BL6 male skin.[13] In humans, it has been recognized for several years that minor histocompatibility antigens can be immunogenic from observations based on organ graft rejections and bone marrow graft-versus-host reactions in cases of genetically matched HLA antigens. A few cases of donor-directed, HLA class I-restricted, cytotoxic T-cell responses have been demonstrated in such cases.[14,15] Two general families of such antigens have been identified:[16]

1. H-Y antigens are proteins encoded on the Y chromosome. Females of the species may mount an immune response against these proteins.
2. T-cells recognize peptidic antigens corresponding to polymorphisms among autosomal proteins expressed by individuals of the species. Examples include mitochondrial proteins and enzymes.

In the presence of both major and minor incompatibilities, it is clear that the alloimmune response targeted against the MHC molecules predominates.

Several studies reported a detrimental role for minor H antigen-specific T-cells in graft survival. However, some data show that minor H antigens might also be clinically involved in preventing rejection of solid organ grafts, possibly by induction of regulatory T-cells.[17]

ABO Blood Group Antigens

The A and B groups are glycosylated differentially, whereas group O lacks the enzymes necessary for glycosylation. The antigens are readily recognized by natural antibodies, termed "hemagglutinins" because they cause red cell agglutination. They are relevant to transplantation because they are expressed on other cell types, including the endothelium. Thus, they cause hyperacute rejection of vascular allografts due to preformed natural antibodies. Allograft rejection due to red blood cell type mismatching can be readily prevented by routine blood typing before transplantation. The rhesus (Rh) factor and other red cell antigens are of little concern because they are not expressed on endothelial cells.

Monocyte and Endothelial Cell Antigens

Occasionally, allografts undergo hyperacute rejection, despite appropriate ABO matching. Some of these rejection episodes have been attributed to additional non-ABO antigens expressed on endothelial cells (such as MICA) and monocytes,[18,19] but these antigen systems remain poorly understood. Pretransplant tissue typing does not currently evaluate the endothelial/monocyte antigens, owing to the apparent rarity of such antibodies and the lack of accurate reagents for typing.

B. Cellular Events Leading to Allograft Rejection

In the context of allograft rejection, T-cells play a central role in orchestrating the immune response, as they recognize alloantigens through two distinct nonmutually exclusive pathways (see following). Once activated, they secrete cytokines and chemokines to activate and attract various effector cells, such as $CD8^+$ T-cells and macrophages into the allograft. They are also able to interact with B-cells that will secrete highly specific alloreactive antibodies. These cells in turn mediate the effector mechanisms of allograft destruction (see following). Table 32-1 summarizes the steps leading to allograft rejection. Furthermore, while T-cells alone are necessary and sufficient for the rejection of allografts, evidence is accumulating about the role of the innate immune system in allograft rejection and prevention of tolerance.

Allorecognition Pathways

The first step in an alloimmune response is the recognition of alloantigens by T-cells (priming of alloreactive T-cells). In the setting of a transplant, there is the potential for two different cellular mechanisms of allorecognition; these have been called the "direct" and "indirect" pathways of allorecognition (Figure 32-5).[20–22]

TABLE 32-1 Steps in Allograft Rejection

1. Recognition of the alloantigen (direct and indirect pathways)
2. T-cell and B-cell activation, differentiation, and expansion
3. Effector functions
4. Resolution of the response with residual memory

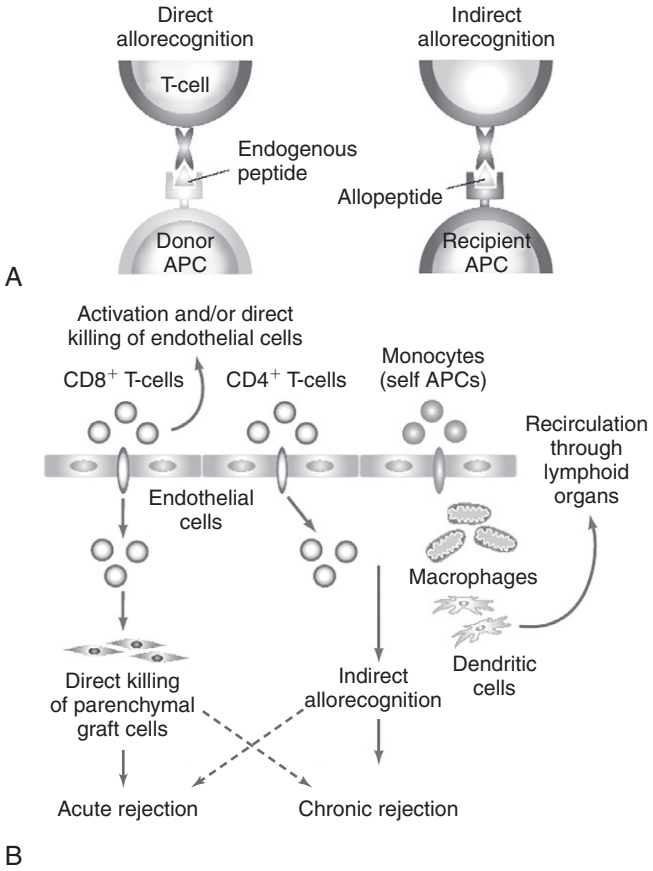


FIGURE 32-5 Allorecognition pathways and graft rejection. **A,** Graft rejection is initiated by $CD4^+$ T-cells, which recognize alloantigens. In the "direct" pathway of allorecognition, the T-cell binds to a major histocompatibility complex (MHC) molecule on donor antigen-presenting cells *(left)*. In the "indirect" pathway, the foreign MHC molecule is processed into allopeptides, which are presented to the T-cell by self antigen-presenting cells *(right)*. Activated $CD4^+$ T-cells proliferate and secrete a variety of cytokines that act as growth and activation factors for $CD8^+$ cytotoxic T-cells, B-cells, and macrophages. **B,** Interactions among endothelial cells, T-cells, and recipient antigen-presenting cells in allograft rejection. Recipient monocytes are recruited by endothelial cells to the graft tissue. They are also transformed to become highly efficient antigen-presenting dendritic cells that may need to recirculate to peripheral lymphoid organs for maturation. The dendritic cells and intragraft macrophages present donor peptides via the indirect pathway to recruited $CD4^+$ T-cells. $CD8^+$ T-cells, on the other hand, are activated by donor endothelial cells and can either directly kill endothelial cells or traverse the endothelium and kill parenchymal graft. (Adapted from D.M. Briscoe, M.H. Sayegh, A rendezvous before rejection: where do T-cells meet transplant antigens? Nat. Med. 8 (3) (2002) 220-222.)

Direct refers to cell recognition of a whole, intact foreign MHC molecule on the surface of donor cells. Although the specific peptide (typically derived from endogenous proteins, including MHC antigens) bound in the groove of the MHC molecule may be important in this recognition process, it does not restrict this response. The graft, which includes donor bone marrow–derived APCs, usually expresses several class I and class II MHC molecules that differ from the recipient's MHC molecules, and which can directly stimulate recipients T-cells. In sum, donor APCs prime $CD4^+$ and $CD8^+$ T-cells through the direct pathway.

However, as these donor APCs are destroyed during the priming process, direct T-cell priming is likely to be time-limited. Thus, direct allorecognition may account for early acute cellular rejection. Consistent with this idea, direct alloreactivity was not detectable in the peripheral blood of a cohort of renal allograft recipients with chronic allograft dysfunction several years after transplantation.[23,24] In contrast, *indirect* refers to T-cell recognition of nonself MHC-derived peptides (allopeptides) in the context of self MHC molecules expressed on recipient APCs. In this case, similar to the physiological pathway of antigen recognition, the peptide sequence determines the response. Indirect presentation could occur through a number of mechanisms: soluble donor MHC molecules are shed from the graft and drain through the bloodstream/lymphatics to the recipient secondary lymphoid organs, where they would be processed/presented by recipient APCs to recipient T-cells. Alternatively, donor graft cells that migrate to recipient secondary lymphoid organs could be endocytosed by recipient APCs. Third, recipient monocyte/macrophages entering the donor graft could endocytose donor antigens and present the peptides to recipient T-cells. Other allopeptides may be derived from minor histocompatibility antigens or tissue-specific antigens. Because recipient monocytes migrating through the allograft can constantly endocytose donor antigen, priming through the indirect pathway could occur for as long as the graft is present in the host. Thus, while indirect alloreactive T-cells may participate in acute rejection, they may play a predominant role in chronic rejection.[25] Consistent with this concept, several groups have now provided data correlating the indirect alloreactive T-cells with the presence of chronic allograft dysfunction.[26–28] Interestingly, recent emerging data demonstrate that not only $CD4^+$ T-cells, as traditionally thought, but also $CD8^+$ T-cells can be primed through the indirect pathway of allorecognition and contribute to graft destruction.[29]

Endothelial cells of donor origin are located at the interface between the recipient's blood and the allograft and have been implicated in graft rejection (see Figure 32-5).[21,30] Graft endothelial cells express MHC class I and II molecules and have been shown recently to promote direct allorecognition by serving as APCs and as targets for T-cell-mediated cytotoxicity. In addition, endothelial cells may promote indirect allorecognition by a crosstalk mechanism, which involves the recruitment and transformation of recipient monocytes by endothelial cells into highly efficient antigen-presenting dendritic cells.[21,30]

Finally, the question of where T-cells meet the transplant antigens has recently been the target of much study. The site of alloantigen recognition had until recently been believed to be in the allograft itself, but recent data seem to indicate that peripheral lymphoid organs are required for allograft rejection.[31] Whether unprimed T-cells encounter antigens first outside of the allograft in peripheral lymphoid tissue or they migrate to secondary lymphoid organs after they encounter the alloantigens in the graft for further maturation and differentiation remains controversial. Interestingly, primed/effector/memory cells appear to mediate graft rejection independent of peripheral lymphoid organs, suggesting that they are activated by alloantigens in the graft itself.[31]

T-Cell Activation

Allograft rejection is a T-cell-dependent process; animals that lack T-cells do not reject an allograft. In particular, $CD4^+$ helper T-cells appear to be essential orchestrators of the alloimmune response leading to allograft rejection.[32] T lymphocytes initiate the immune response, which ultimately results in graft rejection. In addition, they can function as regulators and effectors in the immune response (see following). As just discussed, allorecognition is the essential initial step for initiation of the cascade of events that results in rejection of the graft (see Table 32-1). The essential cell-cell interactions between T-cells and APCs (donor or self) may involve five classes of receptors: the antigen-specific TCR, the CD4 or CD8 coreceptor, costimulatory molecules, accessory or adhesion molecules, and lymphokine receptors. Members of each class of receptors may present suitable targets for therapeutic and experimental manipulation and are thus discussed next.

T-Cell Receptor-CD3 Complex T-cell recognition of alloantigens on APCs is the central event that initiates allograft rejection.[22,33] The interaction between T lymphocytes and APCs involves multiple T-cell surface molecules and their counterreceptors expressed by APCs. Antigen specificity is determined by the TCR, which recognizes processed antigens in the form of short peptides that are bound to an MHC molecule. Clonally restricted TCRs are made up of two chains. The major TCR is a α, β heterodimer, and a less commonly expressed TCR consists of γ and δ chains. The TCR consists of constant and variable portions involved in binding to HLA and recognition of the specific alloantigenic targets. Although the TCR allows T-cells to recognize antigen-MHC complexes, the cell-surface expression of TCR molecules and the initiation of intracellular signaling depend on a complex of additional peptides known as the CD3 complex. After a given TCR is engaged by alloantigen, the T-cell is activated, and a signal (signal 1) is transduced through the TCR-CD3 complex. As will be discussed following, full activation of T-cells requires two synergistic signals (see costimulatory molecules).

The OKT3 monoclonal antibody binds to the CD3 complex. The mechanism of immunosuppression by OKT3 has at least two components.[34] Within hours after administration, OKT3 causes profound depletion of peripheral T-cells. Because OKT3 is not cytotoxic, the depletion is attributed to sequestration of the T-cells. In addition, T-cells downmodulate the expression of the TCR complex. Thus, after a few days of treatment, by flow cytometry, circulating $CD4^+$ and $CD8^+$ cells can be shown to lack detectable TCR. It is thought that the TCR is internalized by endocytosis or shedding. The modulation of TCR expression is reversible, and after elimination of OKT3, the TCR-CD3 complex is again expressed on the cell surface. Recently, a new generation of anti-CD3 monoclonal antibodies has been generated and is currently being tested in the clinic.[35–37] These antibodies are humanized (OKT3 is a mouse antibody) and nonmitogenic, and thus they may prove to be promising in minimizing some of the side effects of OKT3 mediated by its mitogenic properties.

CD4 and CD8 T-Cell Receptor Coreceptors The two major subsets of T-cells, cytotoxic $CD8^+$ T-cells and helper $CD4^+$ T-cells, recognize processed antigens on MHC class I and II

molecules, respectively. CD4 and CD8 molecules enhance the interaction between the TCR and APCs through the MHC. By binding class II MHC molecules, the CD4 molecule facilitates TCR-CD3 complex-mediated signal transduction and assists the actions of class II MHC-restricted T-cells. Similarly, the CD8 molecule binds to class I MHC molecules and stabilizes the interaction of the class I MHC-restricted T-cell with a target cell–mediating signal transduction. Thus, CD4/CD8^{+}TCR-CD3 complex proteins function together in initiating the signals for T-cell activation. Monoclonal antibodies against CD4 or CD8 molecules inhibit T-cell activation and may be important targets for immunosuppression.

Adhesion Molecules Immune cells gain access to the site of inflammation in the graft from nearby lymph nodes and the bloodstream. Associated with transplantation, alloantigens enter local lymph nodes. APCs, such as dendritic cells and tissue macrophages, take up foreign HLA (indirect allorecognition), or foreign HLA on donor APCs is recognized directly (direct allorecognition). Antigen-specific T-cells are activated, differentiate, divide, and enter the bloodstream.

Immune cells move from the bloodstream into the site of inflammation by a three-step process. First, they roll along the vessel wall through interactions between selectins on the endothelium and receptors on the immune cells. Second, they adhere to vessel endothelium. Third, chemoattractant cytokines (chemokines) are released (Figure 32-6). Adhesion molecules and chemokines are important regulators of rejection and appear to be targets for immunotherapy. Adhesion molecules (integrins) are well known for their ability to facilitate adhesion between cells and between cells and the extracellular matrix. Integrins on T-cells include lymphocyte function-associated antigen-1 (LFA)-1, which interacts with intercellular adhesion molecules (ICAM)-1 and -2; CD2, which interacts with CD58 (leukocyte function-associated antigen-3 [LFA-3]); and very-late-appearing antigen (VLA-4) (CDw49d, CD29), which interacts with vascular cell adhesion molecule (VCAM-1, CD106). These receptors are of two large structural families. The integrins, including LFA-1 and VLA-4, are made up of alpha, beta heterodimers, whereas members of the immunoglobulin superfamily, including CD2, LFA-3, VCAM-1, and the ICAMs, are made up of disulfide-linked "receptor" domains. The inhibition of adhesion cell function has been shown to be immunosuppressive. Previous studies in murine and primate models showed increased graft survival with anti-ICAM-1 monoclonal antibodies; however, in a recent randomized multicenter trial, short-term use of the anti-ICAM-1 monoclonal antibody enlimomab for induction therapy after renal transplantation did not reduce the rate of acute rejection or delayed graft function.[38] The blockade of LFA-1 as an induction treatment, on the other hand, is being studied in the context of preventing delayed graft function after transplantation.[39] Recently, efalizumab, a humanized anti-LFA-1 monoclonal antibody, was shown to be well tolerated and effective at reducing the severity of the disease in patients with psoriasis. Although, initial results in renal transplant patients are promising,[40] the company has recently started a voluntary withdrawal of the drug in the United States, as it has the potential to cause progressive multifocal leukoencephalopathy (PML).

Costimulatory Molecules T-cells require two signals for full activation (Figure 32-7). One signal is provided by the interaction of the TCR with the MHC-peptide complex; the second "costimulatory" signal depends on one or more additional receptor-ligand interactions between T-cells and APCs.[41] The two-signal model has gained enormous support in recent years, defining several costimulatory pathways and is now widely accepted (Figure 32-8).[42] Traditionally, these molecules were broadly grouped into two families based on their molecular structures: the immunoglobulin (Ig) superfamily and the tumor necrosis factor receptor (TNFR) family. The CD28-B7 (from the Ig superfamily) and CD154-CD40 pathways (from the TNFR family) have been studied the longest and described as the critical costimulatory pathways for T-cell activation. Blockade of these pathways has been reported to regulate both autoimmune and alloimmune responses in experimental models and in human disease. However, recent

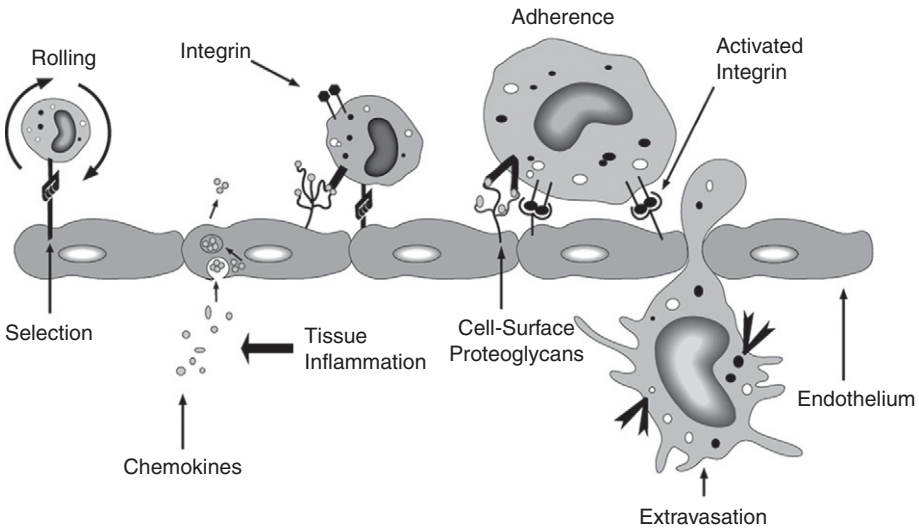


FIGURE 32-6 Three-step model of inflammatory cell migration from the bloodstream into the site of rejection. Rolling of monocytes and T lymphocytes along the vascular endothelium is mediated by selectins. Chemokines may be synthesized by the endothelial cell or produced by tissue cells and subsequently transported across the endothelium. Then they bind to glycosoaminoglycans on the endothelial cell surface, where they can activate leukocyte chemokine receptors, causing integrin activation, flow arrest, and movement across the endothelial cell barrier into the tissues following the chemoattractant gradient. (From V.M. Dong et al., Chemokines and diseases, Eur J Dermatology, 13 (3) (2003) 224-230.)

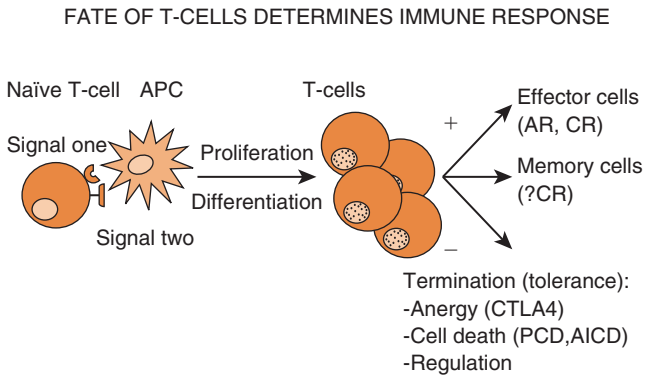


FIGURE 32-7 Stimulation of T-cells through binding of a peptide-MHC complex to the T-cell receptor (signal 1) in the presence of a costimulatory signal (signal two) leads to proliferation and differentiation of these cells. Apoptosis, cell cycle arrest, and active suppression are known regulators of this immune response. A few antigen-specific cells are spared and become memory cells. (From N. Najafian et al., T-cell costimulatory blockade as a novel immune intervention in autoimmune diseases, Clin. Dermatol., 19 (5) (2001) 586-591.)

studies have indicated that inhibition of these pathways is insufficient to reproducibly induce long-lasting immunological tolerance in some experimental autoimmunity and transplantation models, indicating a role for other costimulatory pathways. In fact, the T-cell immunoglobulin mucin (TIM) family of molecules have been recently described as having costimulatory properties (see following).

Emerging data suggest that the costimulatory pathways exhibit some redundancy, hierarchy, and unique functions where various costimulatory molecules affect different T-cell populations and act at different times during the course of the immune response.[42] In addition, a growing number of recently identified negative T-cell costimulatory or coinhibitory pathways have been shown to play an important role in the regulation of T-cell responses.[43] Thus, in the next section, we will first review the role of the most widely studied CD28-B7 and CD154-CD40 pathways in transplantation. Thereafter, we will review some novel emerging data from recent studies about the role of costimulatory molecules in transplantation.

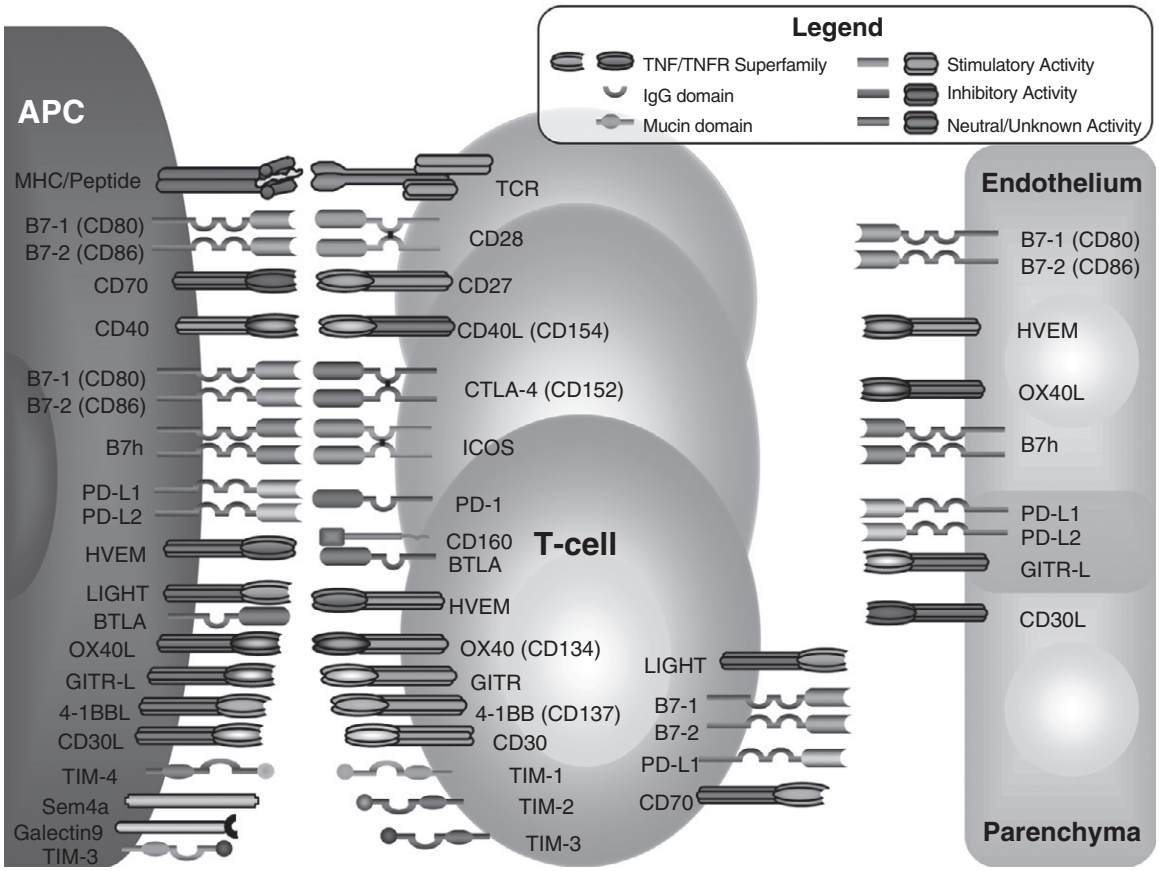


FIGURE 32-8 Overview of the main costimulatory molecules. Costimulatory molecules are depicted in general order of their expression by T-cells *(center column)*, with constitutive expression by naïve T-cells *(top center)*, followed by early activated T-cells *(middle center)*, and effector or memory T-cells *(bottom center)*. Costimulatory ligands expressed by antigen-presenting cells are depicted to the left. Some of these same molecules are also expressed by activated endothelial cells *(upper right)*, parenchymal cells *(lower right)*, or both *(middle right)*. Finally, activated T-cells themselves can express some costimulatory ligands *(center column, right side)*, allowing for additional costimulatory interactions, including those between T-cells. The general structure of various family members is depicted by the presence of immunoglobulin G (IgG) domains (Ig superfamily), trimetric structure (tumor necrosis factor superfamily), or mucin domains (T-cell Ig domain and mucin domain family [TIM] family) of each "stalk." Because costimulatory molecules can have either positive or negative stimulatory function, the effect of each molecule on a particular cell type is depicted by the color of its stalk as red (inhibitory), green (stimulatory), or neutral/unknown (blue or brown). The shape of the ligand-binding region of each molecule designates family membership, and each is color coded to designate each individual molecule. (From X.C. Li et al., Costimulatory pathways in transplantion: challenges and new developments, Immunol. Rev. 229 [2009].)

The CD28/CTLA4-B7 Pathway Many T-cell molecules may serve as receptors for costimulatory signals; the CD28 molecule is the best characterized of these molecules (see Figure 32-8). According to recent gene expression studies, CD28 costimulation can lead to significant augmentation of expressions of genes induced by TCR signaling alone. These findings are consistent with a model of costimulation in which CD28 signaling lowers TCR thresholds for activation of cells.[44] CD28 has two known ligands, B7-1 (CD80) and B7-2 (CD86), both of which are expressed primarily on activated professional bone marrow derived APCs. T-cells also express CTLA-4, a molecule that is highly homologous to CD28 that also binds CD80 and CD86.[44] However, unlike CD28, CTLA-4 transmits an inhibitory signal that serves to terminate the immune response. While CD28 is expressed by both resting and activated T-cells, CTLA-4 is expressed only on activated T-cells. Because CTLA-4 binds B7 molecules with a higher affinity than does CD28, its inhibitory interaction eventually predominates, leading to the termination of the immune response. The importance of CTLA-4 as a negative regulatory T-cell costimulatory molecule in the physiological termination of T-cell responses is highlighted by the observation that CTLA-4 gene knockout mice develop massive lymphoproliferation and early death. One point that needs to be emphasized is the critical role of costimulation in T-cell responses. In the absence of costimulatory signals, sometimes the T-cell simply ignores the peptide-MHC-complex presented to it. At other times, the T-cell undergoes apoptotic death[45,46] or is rendered anergic for up to several weeks; that is, the T-cell is unable to respond to antigens, even when they are presented by APCs that express a costimulatory molecule. Precisely what determines the outcome of the stimulation of T-cell antigen receptors in the absence of costimulation (ignorance, apoptosis, or anergy) is not known. This process is considered one important factor in induction of peripheral tolerance (see following). Thus, manipulation of the CD28/B7 pathway has been envisioned as a potential strategy for achieving therapeutically useful immunosuppression or tolerance. T-cell costimulatory blockade in the form of CTLA4Ig, which blocks CD28 interaction with B7, is currently the most widely used reagent being studied as a means of immunosuppression.[47] To improve the biological potency of CTLA4-Ig, CTLA4-Ig was mutated by substituting amino acids at two positions. The resulting protein LEA29Y (belatacept) had a significantly higher affinity for both CD86 and CD80.[48] The results of a phase II clinical trial demonstrated that belatacept was as efficacious as cyclosporine in preventing acute rejection, was associated with better renal function, and reduced the incidence of chronic allograft nephropathy.[49]

The CD154-CD40 Pathway The CD154-CD40 pathway, initially described as having a role in B-cell activation, has been recognized as a key pathway for T-cell activation as well (see Figure 32-8). CD40 is expressed on APCs, such as B-cells, macrophages, and dendritic cells, and other cell types such as endothelial cells. The ligand for CD40 (originally called CD40L and recently named CD154) is expressed on activated CD4 T-cells. CD154 was later found on stimulated mast cells and basophils and most recently on activated platelets in vitro and in vivo and also in vivo on platelets in the process of the thrombus formation. Stimulation of CD40 provides important signals for antibody production by B-cells and strongly induces B7 expression on all APCs.[50] In this manner, the CD154-CD40 system may have an important role in T-cell costimulation. Activation of APCs through CD40 also induces the expression of adhesion molecules and inflammatory cytokines that participate in T-cell activation. Therefore, CD154 may act in T-cell costimulation by directly providing costimulation, inducing B7, or inducing other costimulatory ligands. CD154-CD40 blockade has been shown to be efficient in preventing acute graft rejection in several small animal models. When an anti-CD154 monoclonal antibody was used as part of a strategy to induce mixed allogeneic chimerism in a renal transplant model, the primates developed donor-specific tolerance. However, some recipients developed thromboembolic complications. Such a complication was also observed in some humans entered in the phase I-II transplant trial with the humanized anti-CD154 (Biogen Inc, Cambridge, MA) monoclonal antibody, resulting in premature termination of trial. Subsequent investigations suggested that these thrombotic events were the result of platelet-derived CD154 either expressed on the surface of platelets or shed in soluble form following platelet activation.[51] Thus, the plans for future development of this agent in transplantation remain unclear. Currently, ongoing studies are focused on exploring alternative approaches to disrupting this pathway such as agents that target CD40.[52]

The Role of Alternate Costimulatory Molecules in Transplantation Other molecules belonging to the TNF superfamily and their receptors (TNF-R), including 4-1BB, CD30, CD134 (OX40), and CD27, and their respective ligands, 4-1BBL, CD30L, CD134L, and CD70, also act as efficient costimulatory molecules for various subsets of T-cells (see Figure 32-8).[53,54] CD134/CD134L blockade might be useful for inhibiting activation of $CD4^+$ T-cells and blunting the function of effector/memory T-cells. In contrast, targeting the 4-1BB pathway may be an attractive approach for manipulating alloreactive $CD8^+$ T-cells. Likewise, the recent discovery of new members of the B7-CD28 family,[53,54] such as inducible costimulator (ICOS) and its ligand B7h, programmed death-1 (PD-1) and its ligands PD-L1 and PD-L2 and B7-H3 and B7-H4 molecules have all been of major interest. Particularly, the latter three pathways (PD1-PDL, B7-H3, and B7-H4) have been recently shown to transmit negative costimulatory signals to T-cells, thus resulting in inhibition of T-cell proliferation and cytokine production either by causing their death or by induction of regulatory T-cells that can inhibit the effector T-cells. These findings imply that the fate of allografts, like allograft rejection or tolerance, are essentially determined by the interplay between positive and negative costimulatory signals.

Costimulatory signals are not restricted to the interaction between T-cells and APC as originally thought, but they also participate in the dialog among T-cells, between T- and B-cells, and between T-cells and nonhematopoietic cells such as endothelial or parenchymal cells. In fact, several studies reveal the importance of the graft tissue expression of negative costimulatory molecule PD-L1 in the regulation of immune responses against allografts.[55]

Finally, the TIM family of molecules possesses costimulatory properties but is distinct from the Ig and TNFR superfamilies (see Figure 32-8). Members of the TIM family are type I membrane proteins with an Ig-variable regionlike and a mucinlike domain.[56] TIM-1 and TIM-2 provide costimulatory signals that promote T helper cell 2 (TH 2)

responses, whereas TIM-3 appears to provide a signal that inhibits Th1 responses. The role of TIM family members in alloimmunity has only recently been investigated and provides a compelling rationale for further investigations in transplantation.[57–61]

In summary, recent studies contributed to a deeper insight into understanding the functions of costimulatory pathways, but complex interactions between simulataneously activated positive and negative costimulatory pathways among themselves, differential expression of these molecules on different subsets of cells such as effector/memory or regulatory cells, and their expression in parenchymal cells of transplanted tissues clearly affect their functions. Further elucidation of these novel concepts offers new opportunities to apply novel targeting strategies of these pathways to the treatment of human diseases in the near future. A major focus of future research is thus directed at dissecting these functions to provide the rationale for developing novel therapeutic targets and strategies for induction of robust and durable transplantation tolerance.

Cytokines/Chemokines. In addition to cell-cell interactions, cell function can be directed through proteins produced by a variety of cell types. These cytokines can function as chemoattractant (chemokines, see following), and growth, activation, and differentiation factors. After antigenic stimulation, $CD4^+$ T-cells differentiate into at least four types of distinct populations: Th1, Th2, Th17, and regulatory T-cells (Tregs, see later), each producing its own set of cytokines and mediating separate effector functions.[62,63] *Type 1* helper T (Th1) cells produce interleukin-2 (IL-2) and interferon-gamma (IFN-γ) and mediate the activation of macrophages and the induction of delayed-type hypersensitivity (DTH) responses (see following). *Type 2* helper (Th2) cells produce IL-4, IL-5, IL-10, and IL-13, which provide help for B-cell function. However, the functional segregation between the Th1 and Th2 subsets remains incompletely understood. Studies with specific Th1 or Th2 cytokine gene-knockout animals indicate the complexity of the Th1-Th2 paradigm in graft rejection and tolerance.[63–65] Data from animal and human studies showed that Th2 clones propagated from patients with stable renal transplant function, or animals tolerant to kidney transplants, can regulate a proliferative response from Th1 clones isolated from patients or animals undergoing active rejection.[66,67] Recent elucidation of a novel lineage of Th17 cells[68,69] has shed light on some of the seemingly inconsistent findings in models of Th1 mediated auto- and alloimmunity where the validity of the Th1/Th2 paradigm has been questioned. IL-17 is a potent proinflammatory cytokine that induces chemokine expression and leukocyte infiltration and mediates tissue inflammation. IL-17 has been implicated in various models of immune-mediated tissue injury, particularly in the absence of a Th1 environment. Our studies have extended this novel paradigm to the transplant setting, enabling us to explain transplant rejection by inflammatory processes mediated by Th17 cells in the absence of Th1-dominant immune responses and demonstrated that CD4 Th17 cells mediate cardiac allograft vasculopathy,[70] while CD8 T17 cells mediate resistance to cardiac allograft tolerance by costimulation blockade.[61] Indeed, IL-17 has been implicated in both experimental and human renal and lung allograft rejection.[71,72] Further, IL-17 neutralization promoted experimental cardiac allograft survival.[73] Except for blockade of the IL-2R, therapeutic strategies in patients that specifically modulate lymphokines have not proved highly effective. Therefore, although manipulation of lymphokine functions may hold promise as a therapeutic modality, we will have to better understand the role of lymphokines in graft rejection and tolerance under physiological conditions if we are to develop effective treatments.

Chemokines are *chemoattractant cytokines.*[74] They are structurally related by amino acid homologies and, in particular, by the placement of cysteines. The nomenclature of chemokines is becoming increasingly complex. Four chemokine families are now recognized, with the majority of members belonging to the C-C chemokine family, represented by RANTES, or the C-X-C chemokine family, typified by IL-8. In general C-C chemokines attract monocytes and T lymphocytes, and C-X-C chemokines attract granulocytes. Detection of altered chemokine mRNA in experimental models of rejection suggests that they play an important role in this process, but because of redundancy and differences in the functions of chemokines in rodents and humans, for the most part the exact role that individual chemokines play in an alloimune response remains unclear. Nevertheless, recent studies in organ transplantation models in knockout animals and with blocking antibodies indicate key roles for the receptors CXCR3 and CCR5 and selected targeting chemokines.[75,76] Mean cardiac allograft survival of 58 days in CXCR3–/– compared to 7 days in the wild-type underline these findings. Similar effects on graft survival were obtained using an anti-CXCR3 antibody in CXCR3+/+ recipients. MHC disparate cardiac allografts transplanted into CCR5–/– mice show a tripling of graft survival. While chemokine expression in the heart is primarily by EC or infiltrating mononuclear cells, kidneys have a heterogeneous population of resident cells, which express inflammatory chemokines when stimulated. Further studies of these knockout mice in studies on renal transplantation will help prove the applicability of these data to renal transplantation.

The Imate Immune System in Allograft Rejection and Tolerance Historically, the focus of transplant immunology has mainly relied on targeting the mechanisms of specific (adaptive) immunity. However, there are emerging data that both rejection and tolerance are influenced by both nonspecific (innate) and adaptive immune responses.[77,78] Factors such as ischemia-reperfusion injury, donor criteria, and brain death serve as danger signals activating the innate immune system. Toll-like receptors (TLRs), natural killer (NK) cells, dendritic cells (DC), monocytes, and soluble components of the innate immune system such as complement are the key players after activation of the innate system.

TLRs are expressed on the surface of various cells, and their engagement is associated with the production of a significant cytokine release, serving to recruit and activate neutrophils and macrophages as part of the innate immune defense system, which in turn has been shown to activate the adaptive immune response. NK cells play a multifaceted role in allograft rejection. Although NK cells contribute to graft rejection and play an important role in promoting adaptive immune responses, they do not seem sufficient to reject solid organ transplants. DCs are also members of the innate immune system and are present mainly in tissues. DCs in lymphoid organs remain in an immature or

semimature steady state until inflammatory stimuli instigate a complex maturation process, allowing alloantigen presentation. Activated DCs recruit NK and T-cells, which then secrete IFN-γ and other inflammatory cytokines that trigger the adaptive immune response. Finally, several other studies have demonstrated that monocytes can precipitate acute rejections after use of T-cell depleting agents in renal transplant recipients.[79,80] Another study demonstrated that the presence of monocytes/macrophages in the follow-up biopsies is one of the factors that may be associated with a bad outcome after AMR.[81] All in all, these studies suggest a pathogenic role of monocytes in allograft rejection.

It is clear that innate immune mechanisms are responsible for the initial inflammatory events following engraftment. While by themselves they are not sufficient to cause graft rejection itself, they are important for optimal adaptive immune responses to the graft and may play a major role in resistance to tolerance induction (see following).

Effector Mechanisms of Allograft Rejection

Transplant rejection has both cellular (DTH responses, cell-mediated cytotoxicity) and humoral components. Once fully activated via the direct or indirect pathway (see preceding), T-cells produce cytokines and chemokines that orchestrate various effector arms of the alloimmune response. The effector mechanisms that are primarily responsible for the rejection process classically involve *Th1 CD4$^+$ T-cells*, *cytotoxic CD8$^+$ T-cells,* and *antibodies.*[82] However, recent experimental studies revealed alternative mechanisms of rejection that implicate *memory T-cells* (see following), and cells belonging to the *innate immune system* including NK cells, eosinophils, and neutrophils. Furthermore, local inflammation associate with rejection is tightly regulated by *Tregs and mast cells* (see section about tolerance).

Primed CD4$^+$ T-cells can provide help for production of alloantibody and can also provide helper signals required for the induction of CD8$^+$ CTLs,[32,33] both of which can subsequently mediate graft injury. Moreover, CD4$^+$ T-cells capable of recognizing donor antigens on donor cells can directly mediate acute graft rejection,[83] but there is some evidence that this outcome is frequency-dependent.[84] Below a certain frequency threshold, primed T-cells may not reject the transplanted organ but may alternatively be capable of inducing chronic injury that results in fibrosis and vasculopathy, characteristic of chronic allograft dysfunction.[85] Furthermore, directly primed Th1 cells and macrophages can mediate DTH reactions and contribute to the destruction of the graft. In that setting, it is hypothesized that some of the cytokines produced by T-cells and macrophages (TNF-α) may mediate apoptosis of graft cells. The pathology of a transplanted organ may also be dependent on the specific graft cell with which the primed T-cells interact. It is tempting to speculate that direct recognition of donor endothelial cells by primed CD8$^+$ T-cells may participate in those acute rejections associated with pathologic evidence of vasculitis.[86] On the other hand, if intragraft donor parenchymal cells are the predominant targets of the direct alloresponse, acute rejection may appear as the classically described mononuclear cell infiltration with tubulitis. Analogous to T-cells functioning through the direct pathway, indirectly primed CD4$^+$ T-cells preferentially differentiate into a proinflammatory type-1 cytokine-secreting phenotype[87] and enable helper signals to induce alloantibodies and cytotoxic CD8$^+$ T-cells that are capable of injuring the graft.[88–90] In addition, indirectly activated T-cells are capable of mediating DTH, and DTH is associated with both acute and chronic graft injury.[91,92] One important question currently under investigation is whether indirectly primed, proinflammatory T-cells can injure a graft even though they cannot interact with any antigen expressed on the graft cells. With skin graft models, it is possible that recipient-derived vascular endothelial cells found on vessels feeding the graft may act as targets of the indirectly primed immune response.[93] The frequency of activated cells may also influence the eventual outcome. Higher frequencies of indirectly primed CD4$^+$ T-cells seem to be associated with acute rejection, while lower frequencies may mediate fibrosis and vasculopathy.[83]

In summary, the pattern of transplant rejection is not only influenced by the T-cell recognition pathway but also by the frequency, the induced effector functions, and the specific cellular targets of the alloreactive T-cells.

B lymphocytes express clonally restricted antigen-specific cell-surface receptors, called *immunoglobulins*.[94] When cell-surface immunoglobulin binds specific antigens in the context of soluble helper factors (such as IL-4, IL-6, and IL-8), B-cells are activated. They differentiate, divide, and become plasma cells that secrete soluble forms of antigen-specific antibodies displayed on their cell surface. These antibodies, in turn, can bind allogeneic target antigens and induce graft damage by binding complement or by directing antibody-dependent cellular cytotoxicity. Beside their involvement in the synthesis of alloantibodies, B-cells also contribute to rejection by other mechanisms, since the benefits of rituximab treatment do not correlate with reduction of alloantibody levels.[95] B-cells infiltrating the graft may actually present graft-derived peptides and contribute to local activation of alloreactive T-cells through the indirect pathway of allorecognition.

Both IgM and IgG alloantibodies can be detected in the serum and in the graft of animals and humans undergoing allograft rejection. Preformed anti-HLA class I antibodies and, occasionally, antiendothelial antibodies play an important role in the hyperacute rejection and accelerated vascular rejection seen in previously sensitized transplant recipients. In the case of xenotransplantation, naturally occurring xenoreactive antibodies play a critical role in the hyperacute rejection of xenografts (see Chapter 36). Finally, alloantibodies against both HLA and non-HLA targets are becoming increasingly recognized as critical in the pathogenesis of acute and chronic renal allograft outcomes.[96] Acute and chronic allograft rejection can occur in HLA-identical sibling transplants, implicating the importance of immune response against non-HLA targets.[97]

Other soluble factors induce additional effector mechanisms, including phagocytosis by granulocytes and macrophages, and cell death by NK cells. NK cells express cell-surface receptors called "killer-inhibitory receptors (KIR)" that recognize HLA class I molecules.[98] When self HLA is recognized, NK cells are prevented from killing. If the killer-inhibitory receptors do not bind to a self HLA molecule, as in certain tumors or viral infections, the target cell is lysed. In addition, NK cells can lyse certain targets expressing nonself HLA (alloantigens). Although NK cells have been identified in rodent and human allografts undergoing acute

rejection, they are neither necessary nor sufficient to drive acute allograft rejection in immunocompetent recipients.[99] It is now thought that NK cells or NK cell subsets do participate in acute rejection of transplanted organs both in mice and humans, particularly when T-cell function is impaired. Although the role of NK cell-mediated cytotoxicity in allograft rejection remains controversial, NK cells appear to play a key role in mediating delayed xenograft rejection (see Chapter 36).

Last but not least, as discussed previously, several other studies have demonstrated that monocytes can precipitate acute rejections after use of T-cell-depleting agents in renal transplant recipients. All in all, these studies suggest a pathogenic role of monocytes in allograft rejection.

Resolution and Memory

Apoptosis, cell cycle arrest, and active suppression are known regulators leading to a dampening of the induced immune response (see peripheral tolerance).[100] Nevertheless, a few antigen-specific cells are spared, and these become memory cells (see Figure 32-7). Memory cells have lower activation thresholds than naïve cells and can respond rapidly to previously encountered antigens. Owing to their survival advantages, rapid reactivation, donor-reactive memory T-cells are now recognized as a serious threat for survival of transplanted organs.[101] Human transplant recipients are likely to harbor alloreactive memory T-cells resulting from direct allosensitization, cross-reactivity to environmental antigens, or homeostatic proliferation as a result of induced lymphopenia by induction treatment. Memory T-cells not only endanger allograft survival by causing both acute and chronic rejection, but recent studies suggest that they impede the induction of transplantation tolerance.[102] Evidence that memory T-cells impede tolerance induction derives from studies using costimulation blockades and mixed allogeneic chimerism strategies.

TOLERANCE

Immunological tolerance to an allograft can be defined as normal graft function and histology in the absence of immunosuppression, associated with the absence of a destructive specific alloimmune response to the graft but with an otherwise fully functional immune system.[103,104] Renal transplantation has been made possible by the development of powerful immunosuppressive drugs that can prevent the rejection process, but usually require lifelong administration, patient compliance, and the risk for a wide range of unwanted side effects. While there has been great success in improving short-term allograft survival in recent years, chronic allograft nephropathy (CAN) remains the principal cause of late renal allograft failure and may even be accelerated by some immunosuppressive drugs. Immunological tolerance would ideally prevent the side effects of immunosuppression and would hopefully prevent chronic rejection, as demonstrated in several animal models.[105] An individual is usually tolerant to self antigens.

Understanding mechanisms of self tolerance has yielded important information regarding the mechanisms of immune responses and has provided the rationale to develop strategies for induction of acquired tolerance. As discussed previously, the T-cell repertoire is modified through negative and positive selection processes in the thymus to delete potentially self-reactive T-cell clones. Self tolerance is partially mediated by "negative selection" through deletion of autoreactive T-cell clones in thymus (central tolerance). On the other hand, potentially autoreactive T-cells that had escaped deletion during intrathymic ontogeny are kept under control by mechanisms of peripheral tolerance. Clonal deletion through apoptosis, anergy, and immunoregulation have all been suggested as nonmutually exclusive and probably complementary mechanisms of peripheral tolerance.[100] Stimulation of lymphocytes through the antigen receptor in the absence of costimulation is not a neutral event and mediates specific inactivation through anergy, a further safeguard against self-reactivity. Thus, it has been suggested that the absence of costimulation on resting tissue APCs could serve to induce and maintain T-cell tolerance to self antigens and that aberrant expression of costimulatory molecules on nonprofessional APCs could activate self-reactive T-cells, resulting in autoimmunity. Recent findings suggest that an additional level of regulation may be achieved by the expression of novel inhibitory molecules (CTLA4 and PD1) on T-cells that can provide negative signals to terminate immune responses.[53]

Similar to self tolerance, the mechanisms of acquired tolerance are listed in Table 32-2. The two types of acquired tolerance are as follows:

1. *Central tolerance* involves thymic deletional mechanisms analogous to self tolerance.
2. *Peripheral tolerance* is mediated by T-cell anergy and deletion, regulatory/suppressor cells, and/or suppressive cytokines.

The occurrence of natural tolerance was first described by Owen, who showed that dizygotic twin cattle that shared a common placenta in utero would continue to have circulating blood cells of their twin specificity after birth.[106] The resultant animals were said to be *chimeric*, and they could not reject skin grafts of the other twin in adult life. This was followed by studies by Billingham, Brent, and Medawar,[107] who demonstrated that it was possible to induce mice to accept skin grafts from a different genetic background if the recipient mice were injected while still in utero (or neonatally) with hematopoietic cells of donor origin. This was the first description of acquired tolerance. Neonatal tolerance is thought to be largely due to clonal deletion, whereby T-cells reactive with alloantigen are deleted in the thymus, presumably by the same mechanisms that delete self-reactive T-cells. Other mechanisms (e.g., immune deviation to Th2 cells), however, have been described as possible mediators of neonatal tolerance.

TABLE 32-2 Mechanisms of Transplantation Tolerance

1. Central tolerance
2. Peripheral tolerance
   a. anergy
   b. apoptosis
   c. regulation (regulatory cells, suppressive cytokines)

Anergy is a state of functional inactivation in which antigen-specific T lymphocytes are present but are unable to respond (by proliferating or producing cytokines) to rechallenge with antigens. Anergy is typically induced when T-cells do not receive a positive costimulatory signal, when positive costimulatory signals are blocked, or when they receive a negative costimulatory signal. Anergy can sometimes be reversed by IL-2 and thus may not be a desirable clinical approach to induce tolerance, since infections may activate the immune system and reverse anergy.

Another mechanism of peripheral tolerance is through the function of antigen-specific *regulatory or suppressor cells*. Such cells have been demonstrated by in vitro assays and by adoptive transfer experiments in vivo.

Natural regulatory T-cells (*natural* Tregs) comprise 5% to 10% of CD4 cells in mice and humans and exhibit potent regulatory activity. They prevent autoimmune diseases, and their depletion can induce de novo autoimmunity in normal mice.[108,109] These cells are selected in the thymus and emerge constitutively, expressing a $CD45RB^{Lo}$ $CD25^{+}$ phenotype. A high proportion also expresses GITR and CTLA-4. While these markers, CD25 in particular, have been extremely useful for identification of natural Tregs, they are also expressed by activated T-cells. Moreover a proportion of natural Tregs lack CD25 expression. Foxp3 is a transcription factor expressed by Tregs that regulates their thymic development.[110,111] In addition to natural Tregs, antigen exposure under various specialized conditions can induce peripheral $CD4^{+}$ T-cells to exhibit regulatory activity. These *induced* Tregs could result from an outgrowth of natural $CD25^{+}$ or $CD25^{-}$ Tregs and may or may not express Foxp3.[108,112,113] More recently, several investigators demonstrated the existence of $CD4^{+}CD25^{+}$ T-cells in the blood of adult healthy volunteers.[114–116] Salama and colleagues provided the first evidence of existence of antigen-specific regulatory $CD25^{+}$ T-cells that are able to suppress alloresponses to donor HLA peptides in stable renal transplant recipients.[117] Therefore, regulatory $CD4^{+}CD25^{+}$ T-cells appear to play a role in the regulation of indirect antidonor alloresponse in stable renal transplant patients. An increase was observed in the frequency of $CD4^{+}CD25high^{+}$ Tregs in peripheral blood of operationally tolerant patients after living-donor liver transplantation compared with those from age-matched volunteers or patients on immunosuppression.[118] Similarly, the blood cell phenotype of clinically tolerant kidney patients displayed normal levels of $CD25hiCD4^{+}$ T-cells and Foxp3 transcripts when compared to healthy individuals.[119] In contrast, recipients with chronic rejection had significantly less $CD25hiCD4^{+}$ T-cells and lower levels of Foxp3 transcript compared with clinically tolerant patients.[119] All in all, these studies demonstrate that Tregs exists in human transplant recipients of various organs and may play a crucial role in the maintenance of allograft function in stable and tolerant patients.

A new, increasingly recognized concept is that Tregs not only have various origins, but like Thcells, they also show plasticity in their development and lineage differentiation. Recent work showed that depending on the cytokine milieu, $CD4^{+}CD25^{+}$ T-cells expanded ex vivo in rats displayed functionally distinct phenotypes peculiar to Th1 and Th2 differentiation pathways.[120] Even more striking is the recent evidence that $CD4^{+}CD25^{+}Foxp3^{+}$ cannot only trigger the expansion of IL-17-producing (Th17) T-cells but even differentiate themselves into Th17 T-cells in vitro in mouse and humans upon stimulation with allogeneic antigen-presenting cells.[121,122] It thus seems likely that in vivo the specific conditions at the site of recruitment of Tregs have a significant influence on their eventual role in the inflammatory process.

To achieve tolerance, the interest in tracking and manipulating Tregs seems obvious (see following). In this context, there is increasing evidence about the impact of currently used therapeutic agents on Tregs frequency and function. For maintenance agents, aggregate data suggest that rapamycin has a more favorable effect than CNI for both frequency and suppressive activity.[123] In the case of induction agents, looking at the proportion of T-cells and especially at the ratio of Teffs/Tregs, it seems that Alemtuzumab and ATG do better than anti-IL2R with maintained potency, suggesting that these former agents might reeducate the immune system.[124–126]

Novel approaches to induce transplantation tolerance in humans include hematopoietic cell engraftment with the goal of establishment of macrochimerism, lymphocyte depletion strategies, costimulatory blockades, and strategies to expand regulatory T-cells ex vivo or in patients.[103] The induction of macrochimerism by marrow transplantation is achieveable only in a small number of patients, as the morbidity of bone marrow transplantation exceeds that of standard immunosuppression in most patients. Thus, investigators have developed strategies to induce mixed chimerism, in which the recipient marrow is largely preserved but modified such that both donor and recipient hemopoietic components coexist. Such transferred hematopoietic cells populate the recipient thymus and marrow and facilitate central deletion of donor alloreactive T- and B-cells. This nonmyeloablative approach has the advantages of being less toxic, preserving immunocompetence and lessening the risk for graft-versus-host disease. One recent paper demonstrated that this is feasible in a patient with myeloma and renal failure.[127] Pilot trials using haplodisparate donor-recipient pairs without underlying malignancy are now ongoing with optimistic preliminary results.[128] Even though promising, mixed chimerism seems to be a practically complex approach to tolerance.

Lymphocyte depletion with polyclonal or monoclonal antibodies has been envisioned as a strategy to reduce nonspecifically the precursor frequency of T-cells, but effector memory T-cells seem to be relatively resistant to depletion. In addition, remaining T-cells after depletion undergo homeostatic repopulation, a barrier to the development of tolerance.

As discussed in detail, there is considerable emerging data that costimulation blockade may facilitate tolerance induction, but important limitations and safety issues need to be considered before Treg-based therapy will become an integral part of clinical armamentarium.

Finally, while the induction of immunological tolerance remains an important clinical goal in transplantation, there are several immunological hurdles that have made it difficult to translate animal studies to humans: these barriers include the large repertoire of alloreactive T-cells in the case of transplantation, the limitations of peripheral immune regulatory mechanisms that are commonly exploited to induce tolerance (T-cell

deletion, anergy, and suppression), cellular and humoral components of the innate immune system leading to inflammation, and the difficult task of "tolerizing" memory T-cells.[102]

SUMMARY

In this chapter, we highlighted our current understanding of the cellular and molecular mechanisms involved in transplant rejection and acceptance. This information has been important in the design of current therapies and may help usher in a new generation of approaches that will result in immunological tolerance, the ultimate goal of transplantation biologists.

A full list of references are available at www.expertconsult.com.

Chapter 33

EVALUATION OF DONORS AND RECIPIENTS

Colm C. Magee, M.D., M.P.H., F.R.C.P.I.

EVALUATION OF THE LIVING DONOR

Overview and Epidemiology

Live kidney donation is increasingly common in the United States and in other countries. This reflects many factors, including the ongoing shortage of suitable deceased donors, the excellent results achieved with live kidney donation (even between unrelated donors and recipients), and greater physician and public awareness of its benefits. These potential benefits are summarized in Table 33-1. The number of living donor kidney transplants has increased greatly in the United States over the last 20 years (although there has been a slight decrease recently, as shown in Figure 33-1).[1] Interestingly, the percentage of living donors who are unrelated to the recipient continues to increase (see Figure 33-1).[1] The term *emotionally related* (as opposed to biologically related) is sometimes used for such donors.

One major advantage of live kidney donation is that preemptive transplantation (before the need for dialysis) is often feasible. Not only does this avoid complications associated with dialysis itself, but studies have shown it is associated with less acute rejection and better allograft survival.[2] This may reflect the avoidance of proinflammatory effects of advanced uremia or of dialysis itself. Despite the poor matching for human leukocyte antigens (HLA) antigens associated with unrelated donation, outcomes are generally excellent.[1] Such outcomes emphasize the benefits of transplanting a "healthy" kidney with minimal perioperative ischemia and reperfusion injury.

Donor Nephrectomy Techniques

Open nephrectomy is the traditional method. The advantages and disadvantages of this technique are summarized in Table 33-2. For reasons that include patient preference, surgeon preference, and probably marketing strategy, laparoscopic nephrectomy has become the donor nephrectomy method of choice in the larger U.S. transplant centers. This can be done as a full or hand-assisted laparoscopic procedure. The advantages and disadvantages of this technique are shown in Table 33-3. There is some evidence that the perceived advantages of laparoscopic nephrectomy have contributed to the increase in donation rates. However, the rates of early allograft dysfunction may be higher with this technique due to higher intraabdominal pressures required during the procedure, longer warm ischemia times, less experience with the technique, a learning curve, and more manipulation of the renal vessels. One recent metaanalysis did show equivalent recipient outcomes with either retrieval technique.[3] It is

TABLE 33-1 Advantages and Disadvantages of Living Donor Kidney Transplantation
ADVANTAGES
Potential for minimum waiting time on dialysis and for preemptive transplantation
Close HLA matching often feasible
Expansion of total donor pool
Elective surgery
Minimal ischemic damage to allograft
Potential for less aggressive immunosuppression
Excellent allograft survival and recipient survival
Psychosocial benefits to donor
DISADVANTAGES
Psychological stress on donor and family
Perioperative morbidity (wound infection, thrombosis, etc.)
Perioperative mortality (rare)
Potential to excacerbate hypertension, proteinuria, or kidney disease over the long-term

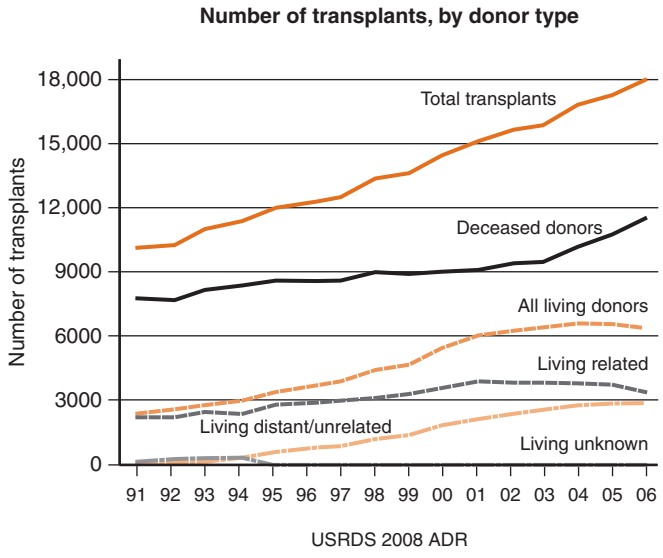


FIGURE 33-1 Number of transplants, by donor type.

TABLE 33-2 Advantages and Disadvantages of Open Nephrectomy for Living Donors
ADVANTAGES
Tried-and-trusted technique; long-term outcomes excellent
Risk of perioperative ischemic damage very low
Retroperitoneal approach minimizes bowel and other abdominal complications
DISADVANTAGES
Relatively invasive surgery
Large scar with risk of hernia

possible, however, that a publication bias exists, with poorer outcomes associated with the newer technique not being reported. One study of UNOS data has suggested that in pediatric recipients, outcomes are inferior with laparoscopically retrieved kidneys.[4]

TABLE 33-3 Advantages and Disadvantages of Laparoscopic Nephrectomy for Living Donors
ADVANTAGES
Less invasive surgery; postoperative recovery faster
Smaller scar
Shorter hospital stay
More acceptable to many donors
DISADVANTAGES
Long-term outcomes not available
Learning curve
Potential for more perioperative ischemic damage and delayed graft function

Choosing the Potential Donor

The general schema for evaluation of a potential donor is shown in Figure 33-2. In general, biologically related donors are preferable to unrelated ones. ABO blood group testing is performed before HLA typing and crossmatching because ABO incompatibility traditionally precludes transplant (a limited number of ABO-incompatible transplants are now being performed). When more than one family member is interested in, and suitable for, donation, the least HLA mismatched donor is preferable. However, older donors, such as parents, are sometimes preferred in case a subsequent transplant might be required. A two-haplotype matched sibling is the ideal donor.

Age

There is no absolute age above which donation is contraindicated. The more important issue is whether there are any medical contraindications (the prevalence of hypertension and type 2 diabetes mellitus, for example, increases with age). A different situation applies in the young where there are major concerns about minors' rights, the ability to freely give informed consent, and the fact that the donor will be exposed to many years of the "single-kidney" state. The majority of centers do not allow donation by those less than 18 years of age (exceptions are sometimes made for identical twins); some centers have higher thresholds, such as 25 years. Unfortunately, there is some evidence that inappropriate donation by minors is occurring.[5]

Safety of Donation: The Risks to the Donor

An important issue in the evaluation of persons for living kidney donation is balancing the professional goal of alleviating the recipient's illness with the philosophy of "first, do no harm." Four conditions must be satisfied before living donation can proceed: the risk to the donor must be low, the donor must be fully informed, the decision to donate must be independent and voluntary, and there must be a good chance of a successful recipient outcome.[6]

The risks are most easily explained to the donor as short- and long-term risks. The short-term risks are those associated with the surgery itself, including death, thrombosis, myocardial infarction, and wound infection. Because donors

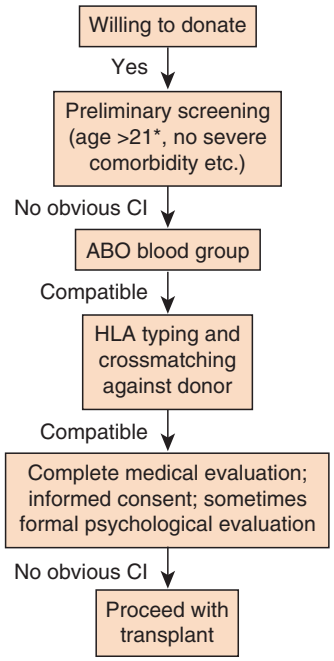


FIGURE 33-2 Typical steps in the evaluation of a patient for live kidney donation. *CI,* contraindication. *Age cutoff varies between programs.

are carefully selected and the surgery is elective, major complications are rare. Perioperative death rates of 0.03% have been reported.[7] Of more concern to the physician evaluating the potential donor are the long-term risks, particularly of higher mortality, hypertension, or kidney disease.

One well-performed European study found that the survival of donors exceeded that of the general population—presumably in large part because only healthy people are allowed to donate.[8] In a recent American study (of predominantly white donors), their survival was similar to that of controls matched for age, sex, and ethnicity. Overall, the data on donor mortality appear reassuring.

Hypertension in the years after donation is not uncommon, but this could reflect factors beyond the effects of the single-kidney state: the natural history in a given donor and/or the assiduous follow-up of donors (with perhaps a low threshold for diagnosing and treating any hypertension). When donors were compared to siblings, a similarly high incidence of hypertension was found in both.[7] The study of Ibrahim and colleagues found the same rate of hypertension—as assessed by the use of antihypertensive drugs—in those more than 20 years after donation compared to controls.[9] However, a recent metaanalysis—which did not include this study—suggested that a 5 mmHg increase in blood pressure occurs within 5 to 10 years after donation above that anticipated with normal aging.[10] Overall, the long-term risk of inducing hypertension after donation does not appear to be excessive—especially if donors are carefully and permanently followed by their physician.

As for other long-term complications, in a subgroup of the preceding study who underwent further evaluation ($n = 255$), 87.3% had normoalbuminuria, 11.5% had microalbuminuria, and 1.2% had macroalbuminuria.[9] The degree of urine albumin excretion in those more than 20 years after donation was actually the same as controls. Previous studies have also suggested that the albuminuria (if present at all) in donors is rarely progressive.

Nephrectomy is followed by a compensatory increase in glomerular filtration rate (GFR) in the remaining kidney to about 70% of prenephrectomy values. Some have expressed concern that GFR would subsequently decline more rapidly in donors. In the study of Ibrahim and colleagues, the iohexol GFR was greater than 60 ml/min/1.73 m^2 in 86% of the subgroup who underwent such testing.[9] End-stage renal disease (ESRD) developed in 11 donors—a rate of 180 cases per million persons per year compared with a rate of 268 per million per year in the general population.[9] Again, the majority of studies indicate that the initial decrement in GFR after donation is not followed by accelerated losses over that anticipated with normal aging.[11]

Although the preceding data, in aggregate, provide reasonable reassurance as to the long-term impact of nephrectomy on donor health, the risks to the donor are not zero, and this fact needs to be strongly communicated to the potential donor. Furthermore, it is very possible that recent donors will have higher rates of nephrectomy-related complications compared to those from 20 years ago because obesity and type 2 diabetes mellitus are now more common in the general population (and will likely become more common in current donors), and some centers are now allowing more "medically complex" donors to donate than before.[12] Ideally, a national registry of donors would be established to allow more rigorous long-term follow-up; this has yet to be done in the United States.

CLINICAL ASSESSMENT OF THE POTENTIAL DONOR

To avoid any conflict of interest, the proposed donor should be meticulously evaluated by a physician who is not involved in the care of the potential recipient. The physician must confirm that the patient's wish to donate is voluntary, which can be more of a concern with nonrelated donors. The physician must also fully explain the short- and long-term consequences of donation. The history, examination, and tests should focus on excluding contraindications to donation. Many of these contraindications are shown in Table 33-4. Not all of these are absolute contraindications, but in general it is better to err on the side of minimizing damage to the donor. Occasionally, disagreements will arise wherein the evaluating physician will advise against donation, but the patient will still want to donate "whatever the risk." A second opinion

TABLE 33-4 Initial Tests for Potential Live Kidney Donors*

CBC, PT, PTT
Plasma creatinine, calcium, urea, electrolytes, LFTs
Fasting plasma glucose (and glucose tolerance test if patient is obese or if family history of type 2 diabetes mellitus)
Chest x-ray, ECG
Renal ultrasound
Estimate of GFR (creatinine clearance or other method)
24-hour urine protein
Urine dipstick and urine culture
Tests for HIV, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, syphilis

*This assumes no ABO blood group or HLA incompatibilities. Imaging studies of the renal vasculature are usually performed later.

TABLE 33-5 Relative or Absolute Contraindications to Live Kidney Donation

Age <18-25 or >70-75 years
Hypertension (BP >140/90 or on antihypertensive medication)
BMI >30-35 kg/m^2
Diabetes mellitus or abnormal glucose tolerance test
History of gestational diabetes mellitus
Malignancy
Significant comorbidity
Microalbuminuria or proteinuria
Recurrent kidney stone disease
Other kidney disease
Low GFR (<70-80 ml/min 1.73 m^2)
Transmissable serious infection (e.g., HIV, hepatitis B, hepatitis C)

is often valuable in such cases. The initial tests in the evaluation of a potential donor are shown in Table 33-5. Imaging of the renal vessels (usually by computerized tomography [CT] or magnetic resonance imaging [MRI]) is often performed last (see Figure 33-2). Potential donors should be warned that occasionally imaging will reveal renal or other abnormalities that may delay or prevent safe donation.

Obesity

Although good short-term results have been reported with the use of obese donors,[13] there is still concern about the long-term risk. Higher body mass index (BMI) has been associated with lower GFR after donation over the long-term.[9] Current guidelines are that those with a BMI greater than 35 kg/m^2 should be strongly discouraged from donating.[14] Those with a BMI of 30–35/m^2 should also be discouraged if they have comorbid conditions. A BMI of 30–35/m^2 in the absence of comorbid conditions (such as impaired fasting glycemia) is not a contraindication, but lifestyle modification should be advised first.

Family History of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is an increasingly common cause of ESRD. Not surprisingly, when the recipient has diabetic nephropathy due to type 2 diabetes mellitus, the risk of related donors developing diabetes later in life is a major concern. Although little is known as to whether single-kidney status would accelerate the progression of diabetic nephropathy, it seems prudent to avoid donation in those thought to be at high risk of developing type 2 diabetes mellitus later in life. In addition to family history (especially first-degree relative) of type 2 diabetes mellitus, other factors that can increase risk are obesity, increasing age, nonwhite ethnicity, and a history of gestational diabetes. All patients with a family history of type 2 diabetes mellitus should have a glucose tolerance test; if this fits the criteria for diabetes mellitus, then donation is prohibited. If the glucose tolerance test is normal and there are no other risk factors, it is reasonable to allow donation. More difficult is where the test is normal but the patient has risk factors in addition to family history for the later development of diabetes. One option is to review the patient again after 3–6 months of lifestyle modification, which has shown to be effective in reducing the risk of progression to diabetes.[15] Another difficult scenario is where tests show impaired fasting glycemia or impaired glucose tolerance: here the risk of progressing to "full" diabetes is high.[16] Unless lifestyle modification reverses the prediabetic state, it seems prudent not to allow donation. Of course, to be effective, lifestyle modification must be continued after donation. It is sobering to note that the estimated lifetime probability of developing diabetes mellitus if born in the United States in 2000 was about one in three.[17]

Hereditary Kidney Disease

When kidney disease in the recipient is due to an inherited disease, it is essential that the disease be excluded in related donors. This will sometimes require close consultation with a geneticist. The most common scenario is a family history of autosomal dominant polycystic kidney disease (ADPKD). If the potential donor is over age 30, the absence of cysts on a carefully performed ultrasound virtually excludes the diagnosis. If the donor is 20 to 30 years old, however, a negative ultrasound does not exclude ADPKD type II (a negative ultrasound or CT are probably adequate to exclude ADPKD type I), and genetic testing such as linkage analysis may be helpful.

Alport syndrome is a genetically heterogeneous disease with X-linked, autosomal recessive and autosomal dominant variants. The majority of cases are X-linked. Screening of donors involves urinalysis, tests of GFR, and specialized eye and ear testing. Male siblings over 20 years of age are very unlikely to have the disease if hematuria is absent. Sisters of affected male recipients with X-linked diseases have a 50% chance of being carriers; a small percent of such females carrying the abnormal gene do develop renal failure. Thus, female heterozygotes (identified as having hematuria but normal renal function) should only be allowed to donate, if at all after detailed consultations with a nephrologist and geneticist.[18]

Hypertension

Potential donors should be carefully assessed for hypertension; 24-hour ABPM is useful in this regard. Any potential donor with hypertension should have an echocardiogram (to assess left ventricular mass), urine protein studies (see following), and a formal ophthalmological assessment (for hypertensive retinal changes). Hypertension with any evidence of end organ damage is an absolute contraindication to donation.[19] Some centers are allowing donation in the setting of "mild" hypertension where there is no end organ damage and where the evaluation is otherwise unremarkable.[20] Short-term results are encouraging, but it must be emphasized that there is a paucity of long-term data in this regard. Close follow-up of such donors after donation is mandatory.

Renal Function

Neither the plasma creatinine or estimated GFR (eGFR) (from the MDRD equation) is a sufficiently accurate measure of renal function in potential donors. Creatinine clearance

(with its well-known limitations) is often used as a measure of GFR. This should be measured at least twice, and the 24-hour urinary excretion of creatinine should be assessed to see if there is under- or overcollection of urine. Some centers use iothalamate clearance routinely or only where the creatinine clearance is low or low-normal. In general, a GFR of less than 80 ml/min or less than 2 standard deviations below normal (based on age, gender, and body surface area (BSA) corrected to 1.73/m^2) should preclude donation.[14] However, factors such as donor age are important in "borderline cases": a decrease in GFR of approximately 1 ml/min/1.73 m^2 per year after age 40 is normal.[14] It should be noted that although adjustment of the GFR for BSA "upward" in a person of low BSA may yield an adequate GFR for donation, the absolute GFR in the recipient will still tend to be low.

Asymptomatic Microhematuria

Urine dipstick testing in the absence of fever, trauma, menstruation, or vigorous exercise should be repeated twice to confirm the presence of microhematuria. Urinary tract infection must be excluded. Urine microscopy should be performed to confirm the presence of red blood cells and to determine whether red blood cell casts are present. If urine protein excretion is increased, donation is prohibited (see following). The presence of unexplained microhematuria at this stage does not exclude donation, but the donor should be informed that further invasive testing is required before he or she can be deemed fit to donate. Cystoscopy, imaging of kidneys and of urinary tract, and kidney biopsy may all be required. The risks of kidney biopsy must be explained carefully to the potential donor. If these tests are normal, the hematuria can be considered benign and donation can be allowed. Occasionally, renal biopsy will be performed and will reveal thin basement membranes or very mild forms of immunoglobulin A (IgA) glomerulonephritis. The prognosis of the former—if there are absolutely no other renal abnormalities and no suggestion of hereditary kidney disease in the family—is generally very good, and some centers will allow donation.[21]

Proteinuria

The urine dipstick is a useful first screening test, but the gold standard test remains the 24-hour urine collection (performed at least twice). Current guidelines are that greater than 300 mg protein per 24 hours is a contraindication.[14] Overcollection of urine should be excluded as a cause of mild proteinuria. Urine albumin is often also measured, but its role in donor evaluation requires further study.

Renal Stone Disease

A history of urinary tract stones is at least a relative contraindication to donation because stones tend to recur and obstruction of a solitary kidney could, of course, be catastrophic. Some centers will consider donation where all of the following apply: passage of only one stone and that at least 10 years prior to donation, no evidence of a metabolic cause (such as hypercalciuria) of stone formation, and current imaging studies showing no urinary tract stones. Any such donors should be advised to continue lifelong high fluid intake. There is some evidence that centers are liberalizing their criteria for allowing those with a history of stones to donate.[22]

Conclusion

Live kidney donation is now commonly practiced in the United States and in other countries. Although the acceptance of more "medically complex" patients as donors is increasing, it is imperative that donors are carefully selected and that the short- and long-term risks of donation are minimized. Ideally, long-term follow-up of donors will be improved; national donor registries would be very helpful in this regard.

EVALUATION OF THE RECIPIENT

Evaluation of the patient with chronic kidney disease for transplantation should begin before initiation of dialysis.[23] This allows preemptive (before dialysis) transplantation if a living donor is available. Even if living donation is not an option, completion of the evaluation and testing means that the patient can be listed for deceased donor kidney transplantation as soon as dialysis is started. The initial evaluation must be thorough (Figure 33-3; Tables 33-6 through 33-8). The patient must be extensively educated as to the risks and benefits of transplantation, and the transplant options (deceased donor, expanded criteria donor, living donor allografts) must be explained. Contraindications to transplant (see Table 33-6) must be

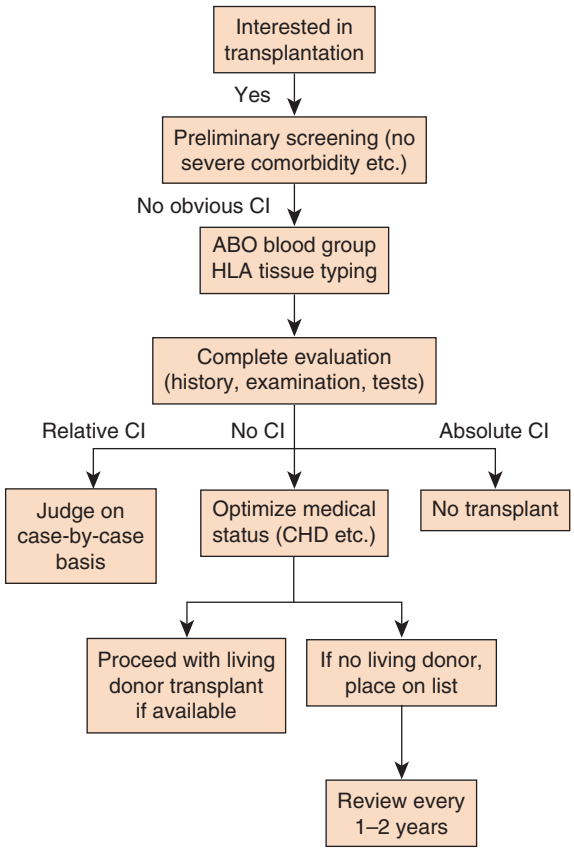


FIGURE 33-3 Typical steps in the evaluation of a patient for kidney transplantation. *CHD,* coronary heart disease; *CI,* contraindication.

TABLE 33-6 Contraindications to Kidney Transplantation

Active cancer
Active infection
Active psychiatric illness
Ongoing noncompliance with dialysis or medicine regimen
Major morbidity that would be worsened by transplant or would lead to very short posttransplant survival
High operative risk
ABO-incompatibility*
Positive T-cell crossmatch*
Severe obesity e.g., BMI >40 kg/m^2

*Protocols are available to facilitate transplantation across these barriers.

TABLE 33-7 Routine Tests for Potential Kidney Transplant Recipients

ABO blood typing, HLA typing, anti-HLA antibodies
CBC, PT, PTT
Plasma creatinine, urea, electrolytes, calcium, phosphate, glucose, LFTs, PTH
Chest x-ray, ECG
Urine dipstick and urine culture
Imaging of kidneys
Tests for HIV, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, syphilis*
If >50 years: stool guaic +/− colonoscopy
Women: Pap smear; mammogram if >40 years
Men: PSA if >50 years

*Testing for additional infections endemic in the area (such as histoplasmosis in certain parts of the United States) may be required.

TABLE 33-8 Additional Tests Sometimes Required for Potential Kidney Transplant Recipients

TEST	COMMENT
Echocardiogram	If any history of heart failure or if there is suspected valvular heart disease
Noninvasive testing for coronary heart disease	If there are additonal risk factors for coronary heart disease
Urodynamics and/or voiding cystourethrogram	If history of reflux nephropathy or chronic pyelonephritis or bladder dysfunction
Imaging of iliac and peripheral arteries	If clinical suspicion of peripheral vascular disease

excluded. In addition to a thorough history and examination, a number of routine tests are required (see Table 33-7). Additional tests required in some patients are shown in Table 33-8. Vaccinations should be administered as indicated (see following).

IMPORTANT ISSUES IN THE RECIPIENT EVALUATION

ABO Blood Group

Because blood group O patients can generally receive only a blood group O allograft (unless some form of conditioning is performed), they tend to wait longer for a deceased donor transplant. One exception to this rule is the use of a living blood group A2 donor for a blood group O recipient. A2 donors have a lower expression of the "A" antigen on the surface of their RBCs and therefore are not as sensitive to the preformed anti–A antibodies present in potential blood group O recipients. Patients with blood group AB have the shortest waiting times, as they have no preformed anti–ABO antibodies. Information regarding the blood group and its implications for waiting time should be communicated clearly to the patient.

TABLE 33-9 New Options for Highly Sensitized Patients

TEST	ADVANTAGES	DISADVANTAGES
Acceptable mismatch programs*	Little extra immunosuppression required	May still involve long waiting time
Donor kidney exchange**	Avoids the need for desensitization; maximizes use of living donors	Logistically complex; may still be hard to find a crossmatch negative donor
Desensitization**	Transplant can proceed relatively quickly; living donor and recipient are biologically or emotionally related	Involves extra immunosuppression; some concern about medium- and long-term outcomes

*For deceased donor kidneys.
**Typically for living donor kidneys.

High Sensitization to Human Leukocyte Antigens

CKD and ESRD patients can develop antibodies against HLA after exposure to these antigens in blood products, pregnancy, or previous allografts. Regular measurement of antibodies to class I and II HLA is now routine in all patients being listed for a transplant. Importantly, the sensitivity of the assays used can vary greatly. Thus, close consultation with the histocompatibility service is essential.

Patients who have antibodies to multiple class I and II HLA (i.e., to multiple donors) are described as highly sensitized. Obtaining a suitable allograft for highly sensitized patients has traditionally proved difficult, and such patients may wait many years for a compatible kidney. Furthermore, rejection tends to be more common and severe. Fortunately, options for highly sensitized patients have improved (Table 33-9).[24] The implications of high sensitization and the options available should be discussed with the patient.

Age

There is no absolute age above which transplantation is contraindicated; biological age is more important than chronological age. Each case should be assessed on its merits. A reasonable criterion is that the patient would be expected to live for at least five years after transplant. Of course, many elderly patients will still need to wait several years before obtaining a deceased donor transplant: regular assessment while waiting is important because of the relatively high chance of new comorbidities developing. Where available, additional listings for expanded-criteria donor kidney transplants should be discussed.

Obesity

Obesity in the transplant recipient is associated with (although not necessarily the direct cause of) more surgery-related complications, more DGF, more cardiovascular disease, higher mortality, and poorer allograft survival.[25,26] Nevertheless, some data suggest that transplantation provides a survival benefit over remaining on the waiting list (on dialysis); no benefit was noted in those with BMI greater than or equal to 41 kg/m^2.[27]

A common approach is to strongly encourage weight loss in all prospective recipients with BMI greater than 30 kg/m^2 and, of course, to rigorously exclude/treat any cardiovascular disease. In those with persistent BMI greater than 30 kg/m^2, eligibility for transplantation is judged on a case-by-case basis; in practice, many patients are eligible, especially if there is minimal comorbid disease. In the very obese who fail to lose weight, it seems reasonable to consider the less invasive forms of bariatric surgery, although only very limited data are available on this topic.[28]

Diabetes Mellitus

It is important to note that diabetics in particular gain a significant survival advantage with transplantation as compared to those diabetics remaining on dialysis on the waiting list.[29] All diabetics transplant candidates should undergo careful screening for cardiovascular disease (by history, examination, and testing), and in general this should be aggressively treated. Patients with type 1 diabetes should also be considered for pancreas transplantation—either simultaneous kidney-pancreas or pancreas after kidney transplantation.[30]

Cardiovascular Disease

The high prevalence of cardiovascular disease in ESRD patients is well-known. It is very important to optimize the cardiovascular status of the transplant candidate before surgery for the following reasons: 1) The stress of surgery and anesthesia can precipitate serious cardiac events such as myocardial infarction, with negative implications for the patient's survival and quality of life; 2) perioperative cardiac events can contribute to delayed graft function; and 3) performing major interventions such as coronary angioplasty/stenting or coronary artery bypass grafting posttransplant could damage the allograft (whereas renal damage is usually not a concern in those on dialysis). Thus, all patients require careful evaluation for clinically significant vascular or coronary heart disease and peripheral vascular disease. A suggested schema is shown in Figure 33-4. Protocols differ substantially between centers; in some, for example, all diabetic patients undergo diagnostic cardiac catheterization. Obviously, consultation with the candidate's cardiologist is important.

Although, in practice, many patients being evaluated for renal transplant undergo noninvasive testing for coronary heart disease (CHD), current guidelines emphasize that a good functional capacity and the absence of acute symptoms of cardiovascular disease predict a low risk of perioperative events in renal transplant surgery.[31] The type of noninvasive test used to screen for coronary heart disease depends on center expertise and availability. In general, an exercise-based (treadmill) test is most desirable, as it best simulates the "stress" of surgery. However, many ESRD patients are not robust enough to achieve adequate heart rates or workloads on the treadmill; in such cases, pharmacological agents can be combined with echocardiography or scintigraphy. The finding of coronary heart disease on noninvasive testing or on coronary angiography *in the absence of symptoms of acute coronary insufficiency* generally does not warrant revascularization; rather, the focus should be on medically managing the risk factors for cardiovascular disease.[31,32] Furthermore, liberal placement of drug-coated coronary stents is not without complications: prolonged therapy with clopidogrel, in addition to aspirin, is required, and many centers will not transplant patients on clopidogrel, since the bleeding risk is high. The use of perioperative beta-blockade in patients known to have coronary heart disease may reduce cardiac events, but the overall benefit is now controversial.[33]

Peripheral vascular disease (PVD) is common in ESRD patients, especially if there is a history of diabetes mellitus. A careful history and examination will identify clinically

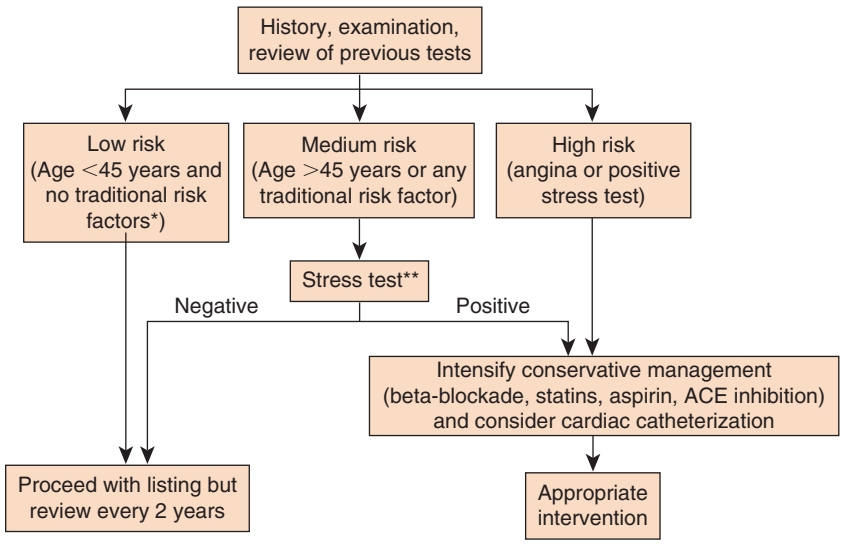


FIGURE 33-4 Suggested evaluation for coronary heart disease pretransplant.
*Hypertension, hyperlipidemia, diabetes mellitus, smoking.
**Specific test will depend on patients's ability to exercise and on local expertise.

significant PVD. Thus, all patients should be specifically asked about intermittent claudication; femoral and lower limb pulses should be palpated and auscultated. Imaging can be performed where the suspicion of PVD is high. Because of concerns regarding the toxicity of gadolinium in CKD/ESRD patients, MR angiography should no longer be used in this setting.

Cancer

At least two years of disease-free status are required for almost all cancers; many programs require 5 years for breast cancer and melanoma. Close consultation with oncology colleagues is essential. Active cancer is a contraindication to transplant for at least two reasons: first, immunosuppression could accelerate progression of cancer, and second, early recurrence with associated morbidity and mortality would "waste" the transplanted organ.

Acute or Chronic Infections

Whenever possible, acute or chronic infections should be eliminated before transplant. In certain situations, complete cure is not possible, and the risks and benefits of transplantation and associated immunosuppression must be very carefully considered. Examples include hepatitis C virus (HCV) infection (response to antiviral therapy is often incomplete) or human immunodeficiency virus (HIV) infection.

BK-Virus

Screening for BK-virus is only indicated in those who have lost a previous allograft from BK-virus infection. The management of such patients is not well-defined. A reasonable strategy is to greatly reduce or eliminate immunosuppression *and* document a consistent fall in blood viral loads to a very low level.[34] Only then should the subsequent transplant proceed. Removal of the infected allograft prior to retransplantation is sometimes performed but does not necessarily prevent recurrence of BK-nephritis.[34]

Hepatitis C

Immunosuppression can accelerate the progression of this systemic disease. This does not mean that HCV-infected patients should forego transplantation. In fact, although HCV-positive dialysis and transplant patients had poorer survival compared to HCV-negative patients, transplantation still conferred a survival benefit over dialysis in those with HCV infection.[35] The management of the pretransplant HCV-positive patient has not been standardized. However, most experts recommend liver biopsy in all transplant candidates to guide prognosis and therapy. The goal, not always achievable, is to eliminate viral replication or, at least, slow progression to cirrhosis. An algorithm for management of the HCV-positive pretransplant patient is shown in Figure 33-5. Interestingly, the response rates to interferon-alfa (IFN) monotherapy are probably higher in dialysis than in nondialysis patients.[36] Ribavirin is contraindicated in those with creatinine clearance greater than 50 ml/min because of its accumulation (due to slower metabolism) and associated risk of severe anemia. One recent series, however, showed impressive rates of sustained virological response when ribavirin was combined with pegylated IFN alfa.[37] The dose of ribavirin was adjusted according to plasma concentrations and to haemoglobin levels. However, use of ribavirin in this setting remains experimental.

Hepatitis B

Transplantation and immunosuppression can worsen hepatitis B virus (HBV) infection. Testing for HBV antigen, HBV surface antibody, and HBV core antibody should be performed in all potential renal transplant recipients. Those who have no

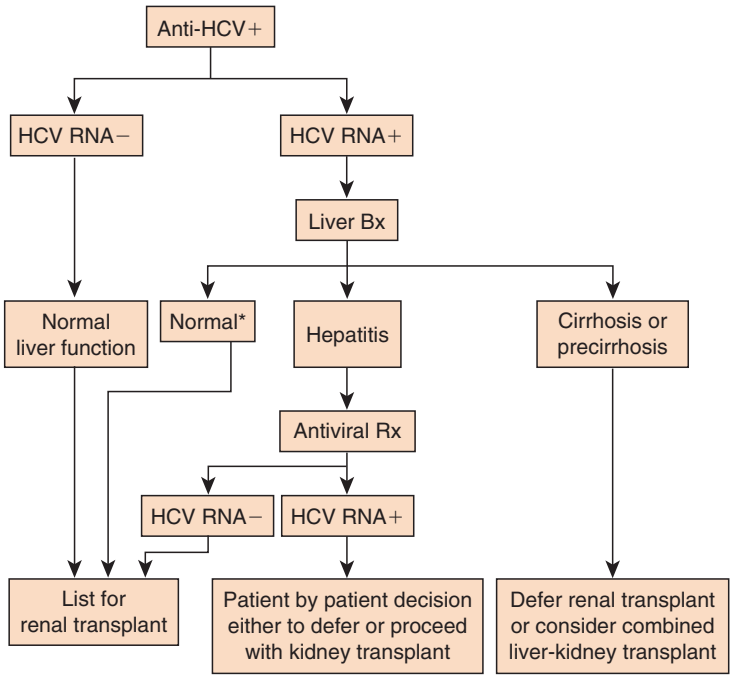


FIGURE 33-5 Management of the anti-HCV antibody positive ESRD patient being considered for kidney transplant.

evidence of exposure to the virus (i.e., surface antibody and core antibody negative) and have not been vaccinated should be vaccinated.

Patients who are HBV surface antigen positive and/or HBV core antibody positive have been infected with the virus and require further blood testing, including LFTS, HBV e antigen, and HBV-DNA. Liver biopsy is sometimes performed to exclude advanced cirrhosis, as this is a contraindication to kidney-alone transplantation. Those patients with active hepatitis are usually treated with antiviral agents before transplant; these agents are resumed after transplant to suppress replication. Typically 18–24 months of posttransplant antiviral therapy is used. Lamivudine has the advantage of relatively low cost and low toxicity but the disadvantage of potential resistance; entecavir is a newer alternative.[38] Those patients without active hepatitis or cirrhosis and without serological evidence of active replication are sometimes treated with antiviral agents *after* transplant. An alternative "preemptive" approach is to monitor serum HBV-DNA regularly and start antiviral agents only when this significantly increases.

Human Immunodeficiency Virus

Until recently, HIV infection was considered an absolute contraindication to renal transplantation in most centers. This reflected fears that immunosuppression would facilitate progression of infection and that the short survival of HIV-positive transplanted patients would waste valuable allografts. With dramatic improvements in the survival of HIV-positive patients, these premises have being reexamined. One difficulty is the potential for interactions among the multiple antiviral medicines, some of which inhibit and some of which induce the cytochrome P450 system. Thus, these patients should be referred to centers specializing in the management of HIV-positive patients, since their management is complex. One recent report showed high rates of acute rejection but not progression of HIV disease in HIV-positive kidney transplant recipients; allograft survival was similar to the general transplant population.[39] More studies are ongoing in this area: see www.hivtransplant.com/.

Tuberculosis

Active tuberculosis, of course, requires full treatment and cure before transplant. Transplant candidates who are PPD positive, regardless of prior vaccination with BCG, and who have no clinical or radiological evidence of active disease should receive a course of antituberculosis prophylaxis if this has not been administered before. Typically, isoniazid is prescribed for 9 months. The major adverse effect of this drug is hepatotoxicity, and monitoring of LFTs is mandatory. Ideally, the complete course of isoniazid is given pretransplant, but posttransplant administration is acceptable.

Ongoing Psychiatric Illness

Psychiatric illness is only a contraindication if it is severe enough to impair understanding of the risks and benefits of transplantation and to prevent normal posttransplant follow-up and compliance. Addiction to alcohol or other drugs should be successfully treated before transplantation. Mental retardation of itself is not a contraindication if adequate posttransplant support is available. The issue of informed consent for surgery, however, can be difficult.

Renal or Systemic Diseases Posttransplant

Certain renal and systemic diseases can recur posttransplant, and in such cases the recipient (*and* the living donor, where there is one) must be informed of this risk. Usually transplantation is not contraindicated, but a waiting period—until the disease becomes quiescent—is sometimes required. In some cases, of course, the cause of ESRD is unknown and recurrence cannot be anticipated.

Primary Focal Segmental Glomerulosclerosis

It is very important to determine the type of focal segmental glomerulosclerosis (FSGS) that has led to ESRD. Familial forms, which are uncommon, rarely recur, and secondary forms do not. However, idiopathic primary FSGS has a reported recurrence rate of about 30% and causes high rates of allograft loss and dysfunction in many such cases.[40] Risk factors for severe recurrence include younger recipients, whites, rapidly progressive FSGS in the recipient's native kidneys, and recurrence of disease in a previous allograft.[40] Because severe forms of recurrence are very difficult to reverse, the patient's risk of this should be estimated, and this risk should be communicated very clearly to the patient (and the living kidney donor, if there is one). Those at very high risk of recurrence (e.g., aggressive and irreversible recurrence in a previous allograft) should probably be offered deceased rather than living donor kidneys.

Anti-Glioblastoma Multiforme Disease

Before transplantation, patients with ESRD due to anti-glioblastoma multiforme (GBM) disease should be on dialysis for at least 6 months and have negative anti-GBM serology. If these criteria are fulfilled, posttransplant recurrence is very rare. *De novo* anti-GBM disease occasionally arises in allografts transplanted into recipients with Alport syndrome; more so if more so if they have had a previous transplant.

Hemolytic-Uremic Syndrome/Thrombotic Thrombocytopenic Purpura

Again, it is important to ascertain the exact form of hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) that leads to ESRD. Recurrence of classical (diarrhea-associated) HUS/TTP is uncommon. Nevertheless, transplantation should be deferred until the disease is quiescent for at least 6 months. In contrast, recurrence of atypical (nondiarrhea-associated) HUS/TTP, particularly if inherited, is very common—about 60%.[41] In general, the prognosis for the allograft is poor if there is recurrence. Fortunately, the genetic defects responsible for many of the atypical forms are now being elucidated. Potential transplant recipients with nondiarrheal HUS/TTP should be tested for these defects, as this information can help estimate the risk of recurrence and guide overall management. Discussion with an expert in this area is recommended. The presence of a complement factor H or I mutation portends a poor outcome for the allograft;

in contrast, outcomes are good for those patients with the membrane cofactor protein (MCP) mutation.[41] At this time, it is debatable whether a kidney transplant alone should be recommended for patients with the complement factor H or I mutation. There are isolated reports of good renal transplant outcomes when (partial) liver transplantation is performed at the same time;[42] the liver allograft synthesizes adequate amounts of the deficient cofactor. However, such an aggressive intervention cannot be routinely recommended until further results are known.

Immunoglobulin A Glomerulonephritis

Studies with longer follow-up have shown that histological recurrence of this condition is common; in one series it was at least 35%.[43] On multivariable analysis, recurrence was not associated with greater risk of allograft failure. IgA glomerulonephritis is not a contraindication to transplant, although it would seem prudent in very aggressive forms of this condition to allow a period of 6 to 12 months on dialysis before transplant.

Systemic Lupus Erythematosus Nephritis

Allograft and patient survival overall are similar in patients with ESRD secondary to lupus nephritis compared to those with ESRD from other causes.[44] Recurrence of severe systemic lupus erythematosus (SLE), systemically or within the allograft, is uncommon after transplant. This probably reflects patient selection, disease activity "burning out" on chronic dialysis, and the effects of powerful posttransplant immunosuppression. Patients should have clinically quiescent disease for at least 6 months before undergoing transplantation. Clinical criteria are a better guide to suitability for transplant than serological criteria alone. SLE patients with antiphospholipid antibody syndrome (APS) probably have poorer allograft and patient survival because of recurrent APS after transplant. These patients should resume appropriate aspirin or anticoagulation therapy as soon as possible after surgery. As patients with ESRD from lupus nephritis have usually received a lot of immunosuppression, particularly steroids, prior to transplantation, it seems reasonable to use steroid-free protocols, at least in low-immunological-risk cases.[45]

Wegener Granulomatosis and Microscopic Polyangiitis

Patient and allograft survival in those with ESRD due to Wegener granulomatosis (WG) or microscopic polyangiitis (MPA) are similar to those with ESRD from other causes.[46] Provided transplantation is performed only when the disease is clinically in remission, rates of relapse (renal or extrarenal) are not excessive. Positive ANCA serology at the time of transplant does not predict later relapse. Even with the latest immunosuppressive protocols, relapse can still occur,[47] although some centers have reported very low rates and excellent outcomes.[48] Relapses usually respond to cyclophosphamide.

Membranoproliferative Glomerulonephritis

The exact form of membranoproliferative glomerulonephritis (MPGN) should be determined prior to listing and transplant. Where the MPGN is secondary (e.g., to chronic infection such as hepatitis C), the infection should be controlled prior to transplant as much as possible; otherwise, recurrence is likely.

Type I (idiopathic) MPGN recurs in up to 50% of cases; the overall incidence of allograft loss at 10 years due to recurrence is around 15%.[49] Type II MPGN tends to recur and cause allograft loss even more frequently. However, the severity of histological change in the native kidneys, rather than the type per se, may be a more important predictor of recurrence.[50] In both forms, recurrence is very difficult to control. Not surprisingly, patients with a history of recurrence are at extremely high risk of recurrence in a subsequent allograft.[51]

Membranous Nephropathy

Membranous nephropathy may recur posttransplant or arise *de novo*. HCV infection and other causes of this glomerulopathy should be excluded. The associated clinical features vary from minimal to nephrotic syndrome. In one series of 30 patients, the actuarial risk of recurrence at three years was 29%, and recurrence was associated with poor allograft survival.[52] This and another more recent study found no pretransplant clinical characteristics that distinguished recurrent from nonrecurrent cases.[52,53]

Primary Hyperoxaluria

Primary hyperoxaluria is a rare inherited metabolic disorder characterized by hyperproduction of oxalate with resultant massive deposition in the kidney and urinary tract. Deposition can recur immediately posttransplant, leading to early allograft loss. The treatment for choice is therefore often combined liver-kidney transplantation as the hepatic allograft corrects the enzyme defect.

Sickle Cell Disease

Many centers consider sickle cell disease a contraindication to transplant. Sickling may actually worsen posttransplant because of the higher blood hemoglobin. Nevertheless, some patients may be candidates for transplantation if the disease is well-controlled and if expert hematological input (for therapies such as exchange blood transfusion) is available in the perioperative period.

Liver Disease

Hepatitis B and C have been discussed previously. General principles related to any liver disease are that transplantation should not be performed where there is active hepatitis or advanced cirrhosis. Less severe forms of liver disease may not preclude transplantation, but wherever possible, treatment should be completed pretransplant.

Diseases of the Gastrointestinal Tract

These are rarely contraindications to renal transplant. Obviously, acute exacerbations of peptic ulcer disease, diverticulitis, and so forth should be treated before transplant. Those with a history of acute cholecystitis should probably undergo cholecystectomy. Some centers perform cholecystectomy in diabetic transplant candidates with asymptomatic cholelithiasis. Sometimes partial colectomy is performed in transplant candidates with recurrent diverticulitis—the rationale again being that recurrence of the disease posttransplant would be more harmful.

Seizure Disorders

Many antiseizure medications upregulate the activity of hepatic cytochrome P450 enzymes. Continuing these medications after transplant may thus lead to difficulty obtaining therapeutic blood concentrations of the calcineurin inhibitors and presumably of other medications metabolized by this enzyme system. Transplant candidates taking antiseizure medications should be assessed as to whether such medications can be stopped or changed to less enzyme-inducing alternatives (for example, carbamazepine is less inducing than phenytoin).

Vaccination before Transplant

If not already immunized or exposed to these microbes, transplant candidates should be vaccinated against hepatitis A, hepatitis B, varicella zoster, measles/mumps/rubella (MMR vaccine), pneumococcus, and diphtheria/tetanus/pertussis (DTP vaccine).[54] These vaccines should be administered early in the evaluation process and well before transplant (live attenuated vaccines should not be given after transplant). With the very high relative risk of urogenital cancers in female transplant recipients, it seems reasonable to vaccinate all young female transplant candidates against human papilloma virus (HPV) according to local guidelines.

MANAGING PATIENTS ON THE WAITING LIST

Waiting times in the United States and elsewhere for deceased donor allografts are increasing; some patients wait for more than 10 years. Thus, dialysis patients are at relatively high risk of developing new complications, particularly cardiovascular disease, while waiting for a kidney transplant. Ideally, all patients on the list, or at least those at highest risk of developing new complications (e.g., elderly, diabetics), should be reassessed every 1 to 2 years. This requires a lot of work. Close communication with the patient's local nephrologist is essential.

CONCLUSION

Thorough evaluation of the potential transplant recipient is essential. The risks and benefits of transplantation and the various transplant options must be carefully explained. As the waiting list grows longer, more attention must be paid to those on the list to ensure that they remain optimally prepared for their transplant.

A full list of references are available at www.expertconsult.com.

Chapter 34

SURGICAL MANAGEMENT OF THE RENAL TRANSPLANT RECIPIENT

Sayeed K. Malek, M.D., F.A.C.S. and Stefan G. Tullius, M.D., Ph.D., F.A.C.S.

A HISTORICAL PERSPECTIVE

Transplantation, one of the most spectacular medical advances of the twentieth century, has fascinated mankind for centuries. Although the modern era of transplantation is just over 50 years old, the legends of transplantation have been recorded in ancient writings since the beginning of time. In Greek mythology, the Chimera was a monstrous creature composed of the parts of several different animals. She had the body of a lion, with a tail that terminated in a snake's head. On her back, at the center of her spine rested the head of a goat.[1] The legend of Cosmos and Damian describes their miraculous feat of transplanting the leg of a dead Moor to an elderly parishioner with a gangrenous limb.[2] Techniques for repairing defects of the nose, ear, and face were first described in the ancient Indian text *Sushruta Samhita*. Tagliacozzi, a 16th-century anatomist and surgeon would use skin from the upper arm to cover an open area on the face (usually the nose), leaving the skin connected to the arm to maintain blood supply.

Advancements in transplantation continued through the Renaissance into the 19th century, but it was not until the 20th century, when techniques for vascular surgery were developed, that the transplantation of vascularized organs was first performed.

In 1902, Emerich Ullmann of Vienna transplanted kidneys into dogs, using metal stents for vascular anastamoses to the carotid artery and internal jugular vein in the neck.[3] At the same time, Alexis Carrel, a young French surgeon, began experimenting with silk sutures and developed a new technique of vascular anastamosis using triangulation and fine silk sutures. He applied this technique to organ transplantation and performed many animal experiments.[1,4] The first human kidney allograft was performed in 1933 by Voronoy in Ukraine.[4] He transplanted a kidney from the victim of a head injury to a patient with renal failure and anastamosed it to the thigh vessels under local anesthesia. The kidney, however, never worked. Stimulated by medical advances, the field of organ transplantation began to develop more rapidly after World War II. Hufnagel and Hume in Boston performed a kidney transplant to the arm vessels in 1946, which worked transiently.

Between 1950 and 1953, human kidney transplants were attempted in Boston and Paris. Despite major experimental and clinical efforts by several teams, little optimism ensued until December 1954, when Joseph Murray of Peter Bent Brigham Hospital in Boston performed the first kidney transplant between monozygotic twins and achieved excellent long-term function. In March 1958, Murray (in Boston) and Hamburger (in Paris) each performed a series of human kidney allografts using total-body irradiation for immunosuppression.[1,3] The modern era of immunosuppression had begun.

INTRODUCTION

Since that first successful transplant of a kidney between identical twins, kidney transplantation has evolved to become the treatment of choice for patients with end-stage renal disease (ESRD). Compared to dialysis, it is associated with increased patient survival and improved quality of life

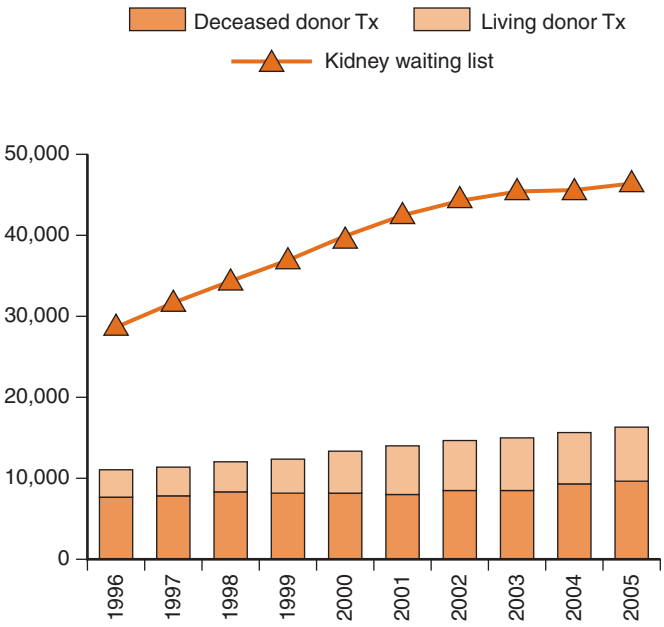


FIGURE 34-1 Kidney transplants at a glance: number of transplants and size of waiting list. From F.K. Port, et al., The 2006 SRTR Report on the State of Transplantation: Trends in Organ Donation and Transplantation in the United States, 1996-3005, Am. J. Transplant. 7 [5] [2007] 1319-1326.)

and with being more cost-effective.[4] The number of kidney transplants in the United States has increased steadily over the past 2 decades, and in 2004 the number of deceased kidney donor transplants in the United States exceeded 10,000. Overall, the greatest increase has been in the number of transplants from living, unrelated donors that increased almost fivefold from 1995 to 2004: from 595 to 2809. Despite these encouraging facts, the number of patients on waiting lists and the wait time for deceased donor kidneys have both continued to rise.[5] According to the United Network for Organ Sharing (UNOS) data, over 72,000 patients are on the decease donor kidney transplant waiting list in the United States (Figure 34-1).[4,5]

PRETRANSPLANT EVALUATION

Prior to transplantation, patients undergo a detailed medical and surgical evaluation.[6–9] The need for dialysis or a creatinine clearance less than 20 ml/min is generally the accepted criteria for placing the patient on the transplant waiting list. The medical evaluation of the transplant recipient is covered in Chapter 33.

A significant proportion of renal transplant recipients have peripheral vascular disease. The surgical evaluation should identify vascular problems that may complicate the transplant procedure. Preoperative imaging such as noninvasive Doppler studies or a computerized tomography (CT) angiogram to evaluate aorto-iliac disease may be required.

A critical component of the preoperative transplant workup is the identification and evaluation of potential living donors. Living donors accounted for 40.8% of kidneys transplanted in 2005. Living donor renal transplantation is associated with improved patient and graft survival[10] and a decreased incidence of delayed graft function. Surgery can be planned as an elective procedure to avoid prolonged waiting times for a deceased organ. The operation is safe, with reported mortality rates of 0.03–0.06%.[11,12] With the more frequent use of laparoscopic and hand-assisted donor nephrectomy, which has been shown to reduce hospital stays, decreasing the use of analgesics, and a faster return to normal activity, an increase in the rate of live kidney donation has been reported.

LIVE DONOR NEPHRECTOMY

Living donor nephrectomy can be performed by either an open approach or laparoscopically. For the open approach, an extraperitoneal flank incision is most commonly employed. However, this technique is associated with considerable morbidity in terms of postoperative pain, duration of recovery, and return to normal activity. Since its introduction by Rattner and colleagues[13] in 1995, laparoscopic donor nephrectomy has been rapidly adopted worldwide in the last decade.

The left kidney is generally preferred for procurement, as the left renal vein is longer and the operation is technically easier than on the right side. In instances where the right kidney is smaller than the left or has a small cyst or a nonobstructing calculus, the right kidney is chosen for donation so as to leave the better kidney with the donor. Careful evaluation of the renal artery and renal venous anatomy is essential before laparoscopic living donor nephrectomy. Spiral CT angiography has become an accepted method for preoperative evaluation prior to laparoscopic donor nephrectomy. More recently, multidetector CT (MDCT) is being used, which provides higher spatial and temporal resolutions. Seventy to seventy-five percent of individuals have a single renal artery bilaterally, with the remainder having two or more renal arteries. In a study of 400 cadaver donors, Pollak[14] found that 23% had two renal arteries, 4% had three, and 1% had four.

Laparoscopic live donor nephrectomy is usually performed via a transperitoneal approach, with the patient in a modified lateral decubitus position. A hand-assisted laparoscopic technique either transperitoneal or retroperitoneal is another alternative and is being used by many centers. Hand-assisted laparoscopy maximizes tactile feedback and allows for easier mobilization of the upper pole of the kidney. It is particularly useful for right-sided nephrectomies because it permits safe division of the right renal vein flush with the inferior cava, thereby maximizing the length of the right renal vein. The kidney can also be retrieved rapidly and atraumatically through the hand port incision without compromising the warm ischemia time.

Initial concerns about ureteric and vascular complications after laparoscopic donor nephrectomy have not been borne out by recent studies. With the refinement of surgical techniques and greater experience, the total (minor and major) donor complication rate has been reduced to 10%–12%, which is comparable to the 8%–20% complication rate for contemporary open donor nephrectomies.[15] Both right-sided kidneys and those with multiple renal arteries can be safely procured laparoscopically.

RENAL TRANSPLANT OPERATION

Patients may arrive at the hospital for a scheduled (living donor) transplant or may be admitted on an urgent basis for a cadaver transplant. Minimization of cold ischemia time to less than 24 hours reduces the rate of delayed graft function, although with current preservation techniques, grafts may remain viable for 72 hours. A complete blood count, electrolytes, prothrombin and partial prothrombin time, and type and cross for ABO compatibility are ordered. Chest x-ray and electrocardiogram are also obtained. The dialysis status of the recipient is determined, and if the most recent dialysis was greater than 24 hours or if hyperkalemia ($K+ > 5.5$) is present, preoperative dialysis may be required. Antibiotic prophylaxis, usually with a first-generation cephalosporin, is instituted.

After induction of general anesthesia, a triple-lumen foley catheter and a central line are inserted. The central line permits monitoring of right heart filling pressures and provides access for blood draws and infusion of intravenous medications and fluid.

The kidney allograft is removed from its sterile container and examined on the back-table to define graft anatomy. Perinephric fat is removed, and the renal artery and vein are inspected. Polar arteries, if present, are identified and may require reconstruction, particularly in the case of a lower polar artery, to prevent ureteral ischemia (Figures 34-2 and 34-3).

The transplanted kidney is placed in a heterotopic location in the right or left iliac fossa, extraperitoneally through a hockey stick incision with minimal muscle-splitting, or the more commonly used Gibson incision, which extends from the midline one finger breadth above the symphysis pubis to a point two finger breadths medial to the anterior superior iliac spine, dividing the external oblique in the direction of its fibers and splitting the internal oblique and the transverses abdominus muscles laterally (Figures 34-4 and 34-5). The inferior epigastric vessels are ligated and divided. The round ligament in females is similarly ligated and divided. In males, the spermatic cord is preserved by retracting it medially. A Bookwalter retractor is then placed to facilitate exposure, and the lymphatics overlying the external iliac vessels are ligatedor coagulated to minimize the risk of lymphocele formation. The iliac vessels are then identified and dissected. The renal artery of the donor kidney is anastamosed either end-to-side to the external iliac artery of the

FIGURE 34-2 Kidney recovered from a live donor.

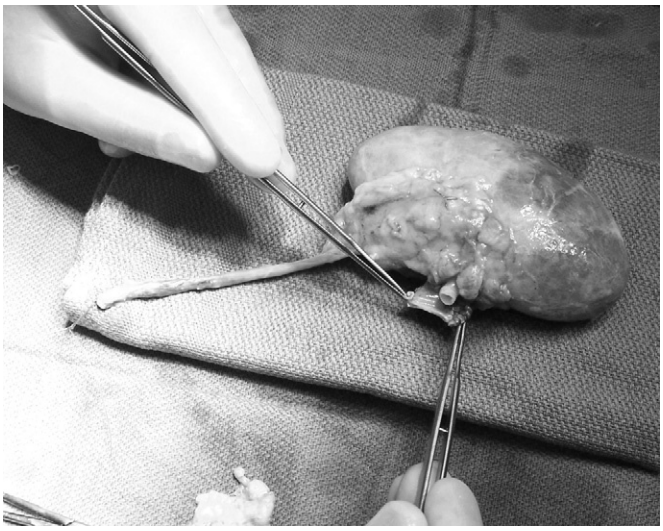


FIGURE 34-3 Kidney after bench preparation with the renal vein dissected.

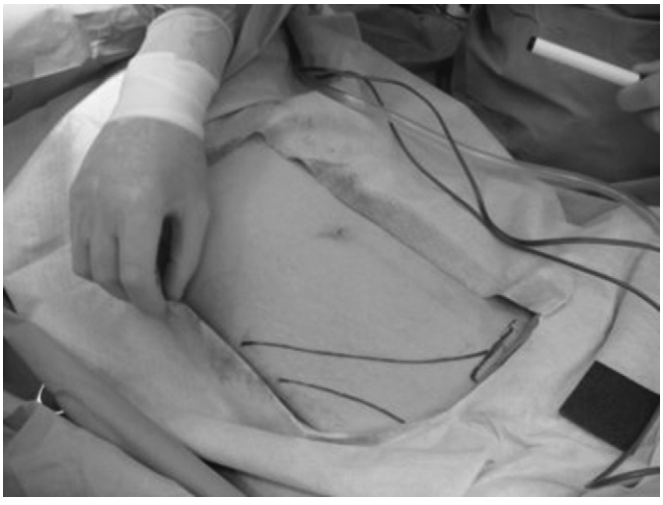


FIGURE 34-4 Incision for kidney transplantation.

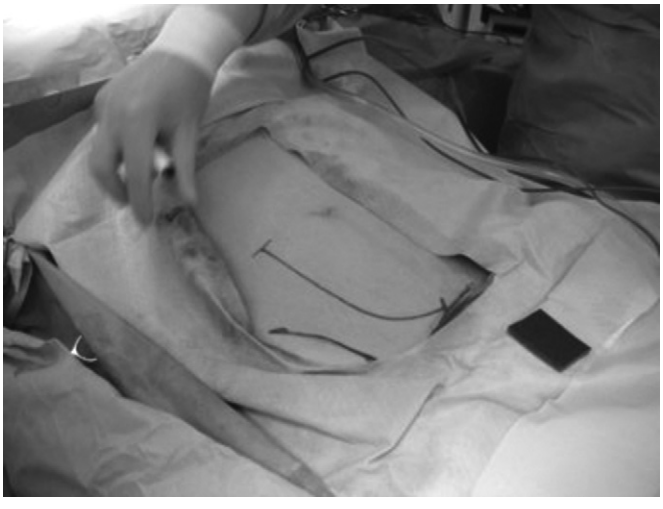


FIGURE 34-5 Optional incision for kidney transplantation.

recipient or end-to-end to the internal iliac artery using 6-0 monofilament sutures. The renal vein is anastamosed to the external iliac vein, also with 5-0 or 6-0 monofilament suture. After revascularization, hemostasis is secured and the patient is given diuretics to maximize perfusion to the allograft. Urinary continuity is established by anastomosing the donor ureter to the recipient bladder (ureteroneocystostomy) or the recipient ureter (ureterouretrostomy) after removal of a native kidney. The former is the commonly used method and can be done by a direct extravesical method or by creating a submucosal tunnel (Politano-Leadbetter technique). A double-J stent is placed across the anastomosis to prevent stricture formation and is removed 6 weeks later by cystoscopy (Figures 34-6 through 34-8).

EARLY POSTOPERATIVE MANAGEMENT

Transplant patients are usually extubated in the operating room and transferred to the postanesthesia care unit. Optimal perioperative management requires careful assessment of volume status. Documentation of brisk urine output provides an indication of early renal function in patients who were anuric prior to transplantation. The initial goal is to keep the patient euvolumic or slightly hypervolumic. However, if the transplant does not function immediately and the patient is oliguric or anuric, a Doppler ultrasound of the transplant should be obtained to rule out decreased perfusion or obstruction. Patency of the Foley catheter should be confirmed and the CVP measured to rule out hypovolumia. Half normal saline is the intravenous solution used to replace urine output. Delayed graft function occurs in 20%–30% of cadaver renal transplants, particularly in donation after cardiac death (DCD) and expanded criteria donors (ECD) kidneys. Hyperkalemia may be a problem in patients with low urine output and should be monitored carefully. When the patient is stable and the early lab results are satisfactory, transfer to a regular transplant floor bed is initiated. Intensive care monitoring is seldom required.

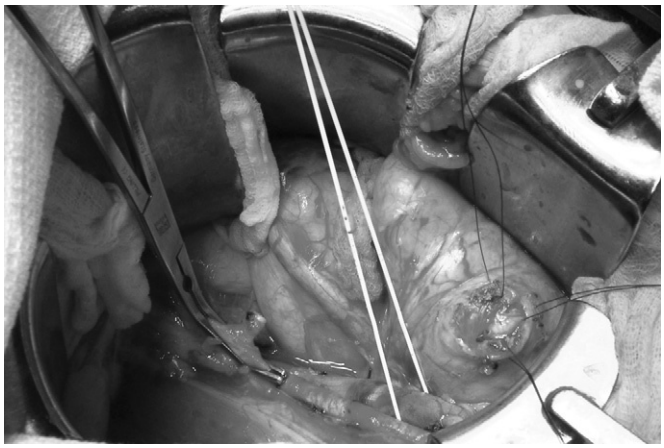


FIGURE 34-6 The illiac vessels exposed. Vessel loop around external iliac vein.

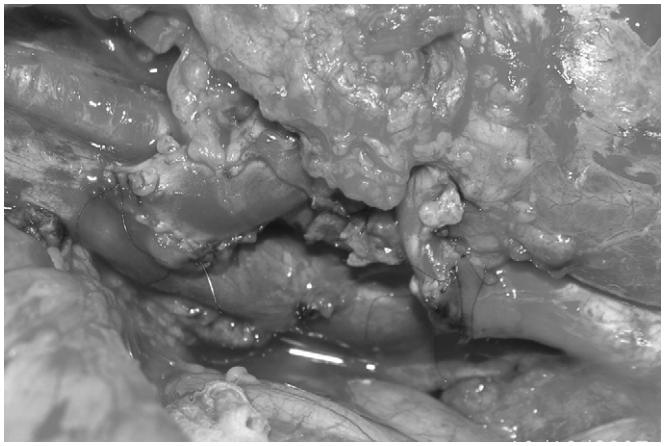


FIGURE 34-7 Arterial and venous anastamoses completed.

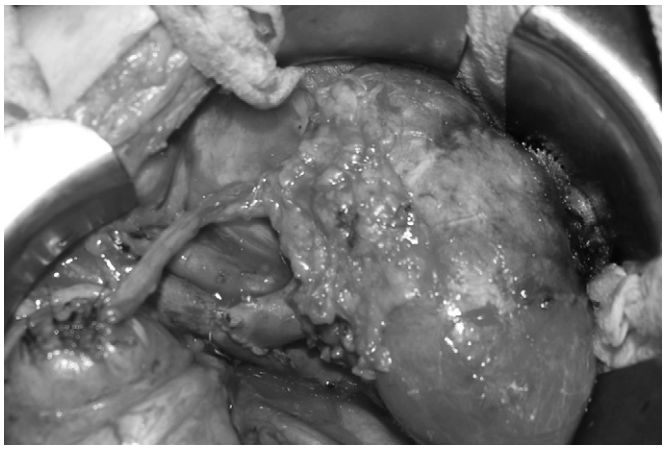


FIGURE 34-8 Ureteral anastamosed to urinary bladder (left foreground).

COMPLICATIONS

Complications after renal transplantation may be surgical or medical. Surgical problems are generally vascular[16–19] or urologic[20,21] and present early after transplantation.

Renal Artery Thrombosis

Renal artery thrombosis is a rare complication with an incidence of 1%, usually the consequence of technical problems during surgery. Possible causes for thrombosis include hypotension, torsion or kinking of the vessels, trauma to the donor artery (unrecognized intimal injury) during organ procurement, hypercoagulable state, donors with multiple renal arteries, disparity in vessel size during anastomosis, and accelerated rejection. Diagnosis is made by Doppler ultrasound, which shows absence of arterial flow. Successful thrombectomy with salvage of the allograft has been reported on rare occasions, but in most cases the allograft will have to be removed.

Renal Vein Thrombosis

This occurs in 1%–4% of recipients and almost invariably results in the loss of the transplant kidney. It may be secondary to technical errors at the anastomosis, resulting in torsion or angulation of the renal vein. Other causes include hypotension, hypercoaguable state, extension of deep vein

thrombosis, and external compression from hematomas or a lymphocele. Clinical signs include a sudden decrease in graft function and pain and swelling over the graft. Diagnosis is established by Doppler ultrasound.

Renal Artery Stenosis

The incidence of renal artery stenosis is reported to range from 2%–10% and is the most common vascular complication seen after renal transplantation. It usually occurs late after transplant from a few months to a year or two posttransplant, but it is occasionally seen early (<7 days). This complication occurs more commonly after living donation, since there is an end-to-end anastamosis of the transplant and native renal arteries as opposed to a cadaveric donor, where a cuff of the donor aorta is removed. It is heralded by the sudden onset of refractory hypertension associated with graft dysfunction. The cause is multifactorial and may be related to technique, kinking or twisting of the anastomosis, or atheromatous changes in the recipient vessels. The gold standard for diagnosis remains the arteriogram, although the initial tests may be noninvasive such as a duplex scan. Magnetic resonance angiography is also used, but with the reports of fibrosing dermopathy associated with the use of gadolinium in patients with compromised renal function, it should be used with caution. Treatment is with percutaneous transluminal angioplasty (PTA), with or without stent placement. Open surgical correction may sometimes be required in selected cases.

Urological Complications

Urinary tract complications occur in 2%–10% of patients and are a common cause of morbidity after renal transplantation. They may manifest as urine leaks early in the posttransplant period when the likely cause is a technical error. The ureter may also be devascularized during organ procurement, producing ischemic injury. Presenting features may include fever, pain, and swelling over the graft; decreased urine output; an elevated serum creatinine; or urine from the incision. Analysis of the fluid for creatinine is a simple method to confirm the presence of a urinary leak. An isotope scan or a cystogram may aid diagnosis. Small urinary leaks usually resolve spontaneously with catheter drainage, but if they are significant, surgical revision of the anastomosis is required.

Obstruction of the urinary tract is most often painless and presents as a rise in serum creatinine. Diagnosis is confirmed by ultrasound examination, which shows hydronephrosis. Early obstruction is commonly from technical errors, and late obstruction is usually a result of ischemic strictures of the ureter. Treatment is with percutaneous nephrostomy, balloon dilation of the stricture, and double-J stent placement. Surgical exploration and repair is reserved for strictures that fail to respond to percutaneous methods.

Lymphoceles

The incidence of clinically significant lymphoceles is 0.6%–18%.[22] They occur as a result of inadequate ligation or coagulation of lymphatics overlying the iliac vessels or leakage of lymph from the allograft. Lymphoceles may compress the transplant ureter or present as unilateral lower-limb swelling. Diagnosis is made with ultrasound examination. The initial approach is percutaneous aspiration and catheter drainage, with an overall success rate of 60%–73%. Instillation of sclerosants such as tetracycline or povidone iodine may be attempted to obliterate the cavity, but this carries the risk of chemical peritonitis if the sclerosant leaks into the peritoneal cavity. Symptomatic persistent lymphoceles are treated surgically by draining the cyst into the peritoneal cavity. This can be done using an open or a laparoscopic approach, with a primary success rate of 90%.

TRANSPLANT OUTCOMES

Patient Survival

The survival of patients receiving a transplant from a living donor is superior to those who receive an allograft from a deceased donor. Unadjusted survival rates at 1 and 5 years, and postliving donor renal transplant are 98% and 90%, respectively. Diabetic living donor recipients have a lower 5 years patient survival of 83% compared to other primary diagnosis groupings, and recipients of kidneys from older donors (>65 years) had a lower patient survival rate (78%) than recipients of younger donor kidneys.

For deceased donor kidney recipients, the 1- and 5-year patient survival rates were 96% and 83%, respectively. The rates for ECD kidneys were 90% and 69%.[10] ECD are defined as all donors older than 60 years or donors older than 50 years with any two of the following criteria: hypertension, cerebrovascular cause of brain death, or a preretrieval serum creatinine (SCr) level greater than 1.5 mg/dl.[23]

Overall, the improvement in posttransplant outcomes has been attributed to improvements in organ preservation, refinement of surgical technique, and the use of newer, more potent immunosuppressive agents.

Graft Survival

Graft survival rates for living donor kidney recipients at 1 and 5 years were 95% and 90%, respectively. African American patients and those older than 65 had the lowest 5-year survival at 72% and 70%, respectively. Graft survival for deceased donor kidney recipients of non-ECD kidney transplants were 90% and 70% at 1 and 5 years. Unadjusted graft survival for ECD transplants was 82% and 53% for the same follow-up period. African American patients continue to do worse than other racial groups, with 46% graft survival at 5 years. Graft survival for DCD kidneys was 87% at 1 year and 65% at 5 years (Figures 34-9 and 34-10).[10]

STRATEGIES FOR EXPANDING DONATION

Living Donations

After growing from 3933 donors in 1997 to 6647 donors in 2004 in the United States, living kidney donation declined slightly to 6436 donors in 2006. There has been an increase

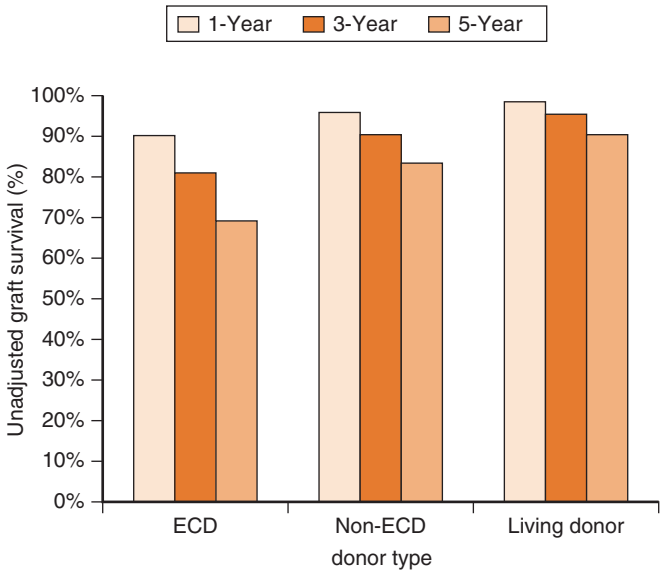


FIGURE 34-9 Unadjusted 1-year, 3-year, and 5-year kidney graft survival by donor type for transplants 1999-04. (From K.A. Andreoni, et al., The 2006 SRTR Report on the State of Transplantation: Kidney and Pancreas Transplantation in the United States, 1996–2005, Transplantation 7 [5] [2007] 1359–1375.)

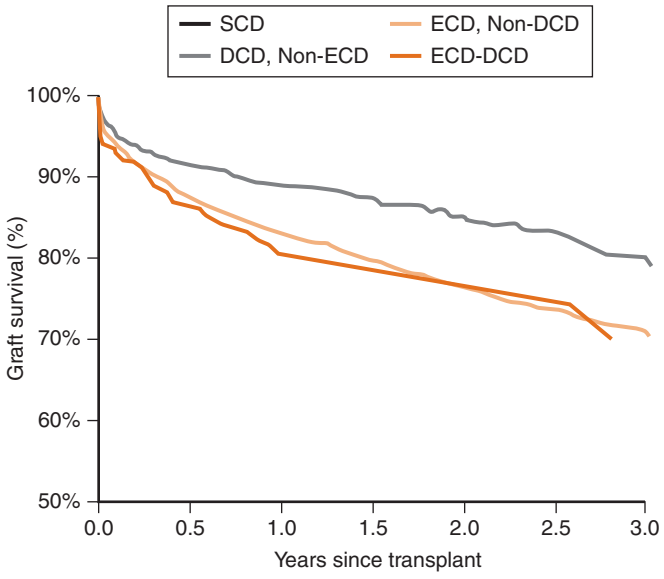


FIGURE 34-10 ECD kidneys, 2000-2004. (From K.A. Andreoni, et al., The 2006 SRTR Report on the State of Transplantation: Kidney and Pancreas Transplantation in the United States, 1996–2005, Transplantation 7 [5] [2007] 1359–1375.)

in unrelated donors, which now represent 24% of all donors.[24] Many willing live donors are excluded from donation because of ABO incompatibility with their intended recipient or from prior sensitization as a result of a previous transplant, blood transfusion, or pregnancies. Novel strategies to permit these patients to receive a kidney transplant are being tried by various transplant centers.

In the mid eighties the concept of kidney paired donation (KPD) was first proposed to allow exchanges between incompatible pairs. Willing kidney donors found to be incompatible with their planned recipient could potentially donate to another, unrelated compatible recipient who also has an incompatible donor, thereby setting up a paired kidney exchange. As of 2008, in the United States, 82 transplants from 24 transplant centers have been reported to the UNOS using this strategy.

Deceased Kidney Donations

As both the numbers of patients who are waiting for a deceased donor kidney and those who die waiting for a kidney increase, the use of kidneys from expanded and DCD donors has increased. Kidneys procured from donors declared dead based on irreversible cessation of cardiac function accounted for more than 6% of kidneys in 2006. Although there is a higher incidence of delayed graft function, both short- and long-term graft survivals are similar to standard criteria (SCD) donors.

With the recovery of more ECD and DCD kidneys, there has been renewed interest in the use of pulsatile machine perfusion not only to improve vasospasm and reduce delayed graft function but also to assess vascular resistance as a method to identify kidneys that may not be suitable for transplantation. Moers[25] and colleagues in a recent study showed that hypothermic machine perfusion was associated with a reduced risk of delayed graft function and improved graft survival in the first year after transplant.

Dual deceased donor kidney transplant of both adult kidneys into a single, older, size-matched recipient has also been attempted in an effort to expand the donor pool. Remuzzi and colleagues[26] reported that dual kidney transplants from donors over the age of 60 could provide 90% 3-year graft survival in carefully selected recipients based on a pretransplant histology score.

Pediatric en bloc deceased donor kidney transplantation is the use of both kidneys attached to the donor aorta and is used by some centers for transplantation of kidneys from donors younger than 2 years old. A primary concern with the use of en bloc kidneys is the increased risk of surgical complications, particularly graft thrombosis.

Horseshoe Kidneys

The incidence of horseshoe kidneys ranges from one in 600 to one in 800. Embryologically, the kidneys fail to rotate medially during development, and the renal pelvis faces anteriorly. There may be associated renal vascular anomalies. The horseshoe kidney is procured en bloc and can be divided at the avascular isthmus and be transplanted into two recipients or into a single recipient if division is not feasible.

CONCLUSIONS

Renal transplantation in the 21st century is the optimal therapy for patients with ESRD. There has been significant improvement in 1-year graft survival, and patient survival rates are excellent. However, the rate of late graft failure remains of concern, with the graft survival half-life for both living and deceased donor transplants showing minimal changes. According to USRDS data, the graft survival

half-life for deceased donor kidney transplants was 11.4 years in 1995 and 10.5 in 2002; for living donor transplants, the rates were 18.4 and 19.1. The number of patients starting or restarting dialysis due to a failed kidney transplant rose from 3752 in 1995 to 5156 in 2004. The exponential growth in the waiting list and an acute shortage of organs continue to pose challenges for the future.

A full list of references are available at www.expertconsult.com.

Chapter 35

BIOLOGICAL AGENTS IN KIDNEY TRANSPLANTATION

Edmund Huang, M.D., Karl L. Womer, M.D., and Flavio Vincenti, M.D.

Biological agents in the form of polyclonal and monoclonal antibodies (MAbs) have been used in kidney transplantation as early as the 1960s, when Starzl and colleagues reported excellent short-term patient survival and kidney allograft function following the use of antilymphocyte globulin (ALG) as adjuvant immunosuppression to azathioprine and prednisone.[1] Whereas Starzl and colleagues administered ALG in periodic intervals over 4 months, later reports used biological agents for induction therapy, limiting their use for rejection prophylaxis to the immediate posttransplant period to avoid complications of excessive immunosuppression. A number of biological agents have been used in kidney transplantation since Starzl's early report. Polyclonal and monoclonal antibodies are now widely used both for induction therapy and for the treatment of rejection (Table 35-1). Current research is focused on using induction therapy to facilitate drug minimization regimens and on developing newer biological agents for maintenance immunosuppression.

The antibodies used in kidney transplantation can be classified as either polyclonal or monoclonal. These can be divided further into two groups: the depleting agents and immune modulators. Several polyclonal antilymphocyte preparations have been used in renal transplantation; however, only two preparations, ATGAM and Thymoglobulin—both T lymphocyte-depleting agents—are currently approved by the U.S. Food and Drug Administration (FDA) for use in kidney transplantation.[2,3] Monoclonal depleting antibodies may be T lymphocyte specific (OKT3, anti-CD3), B lymphocyte specific (rituximab, anti-CD20), or nonspecific (alemtuzumab, anti-CD52). Immune modulators consist of monoclonal antibodies directed against the interleukin-2 (IL-2) receptor (IL-2R MAbs). Examples of IL-2R MAbs include basiliximab and daclizumab, which block IL-2 mediated T-cell expansion by binding to the α-chain of the IL-2R.

The use of polyclonal and monoclonal antibodies for induction has been increasing in popularity, as demonstrated in Figure 35-1 showing the progressive rise in induction therapy usage from 1997 to 2006.[4] This trend coincides with the publication of results from several pivotal prospective double-blinded randomized trials demonstrating lower rejection rates when IL-2R MAbs were used for induction compared to placebo[5–8] and two meta-analyses suggesting that the use of antilymphocyte antibodies was associated with improved graft survival compared to no induction therapy.[9,10] More recently, induction therapy has been used in drug minimization regimens, including calcineurin-inhibitor (CNI)-sparing[11–13] and steroid minimization protocols.[14,15]

The decision to use induction therapy is often based on the clinical evaluation of the immunological risk of transplant recipients. Although many centers now use induction therapy in all recipients, the following categories of patients tend to derive the most benefit from induction:

1. Patients at high immunological risk of rejection (i.e., African Americans, sensitized patients, patients with delayed graft function, retransplant patients)[16]
2. Patients who require or are being considered for CNI-sparing regimens
3. Patients in whom corticosteroids are completely avoided or withdrawn within days after transplantation

The next important decision in induction therapy is the selection of the desired type of biological agent: depleting antibody (Thymoglobulin, Atgam, OKT3, or alemtuzumab) or a non-depleting IL2R MAb. The benefits and side effects of these two groups of biological agents are shown in Table 35-2.

TABLE 35-1 Antibodies Currently Used in Kidney Transplantation

MONOCLONAL DEPLETING	MONOCLONAL NONDEPLETING
OKT3 (T-cell specific; murine; anti-CD3)	Basiliximab (chimeric; anti-CD25)
Rituximab (B-cell specific; chimeric; anti-CD20)	Daclizumab (humanized; anti-CD25)
Alemtuzumab (nonspecific; humanized; anti-CD52)	
POLYCLONAL	
Thymoglobulin (rabbit-derived globulin)	
ATGAM (horse-derived globulin)	

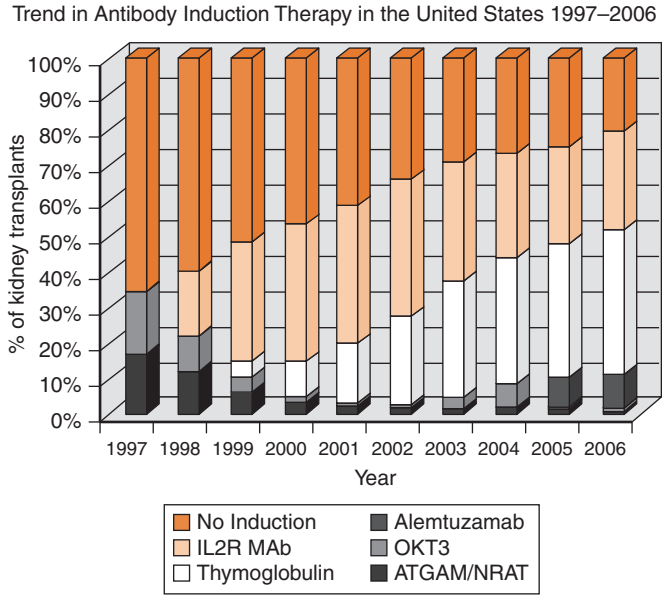


FIGURE 35-1 Trend in antibody induction use in the United States from 1997 to 2006. (Adapted from the *2007 Annual Report of the U.S. Organ Procurement and Transplantation Network* and the *Scientific Registry of Transplant Recipients: Transplant Data 1997-2006*. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD, 2007.[4] The data and analyses reported in the *2007 Annual Report* of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients have been supplied by UNOS and Arbor Research under contract with HHS. The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the U.S. government.)

TABLE 35-2 Pros and Cons of Depleting versus Nondepleting Induction Therapy

DEPLETING ANTIBODIES	NONDEPLETING ANTIBODIES
Rejection rare during use	Rejection may occur during use
Calcineurin inhibitors can be used sequentially (delayed)	Calcineurin inhibitors should not be delayed
Acute side effects with administration	No acute side effects with administration
Associated with increased infections and malignancies	Not associated with complications of overimmunosuppression

The choice of the specific antibody within each class is often arbitrary but may be based on cost, ease of administration, safety, and efficacy. Thymoglobulin may have a beneficial effect on delayed graft function when given before reperfusion, presumably by preventing ischemia-reperfusion injury.[17] Alemtuzumab, a powerful lymphocyte-depleting monoclonal antibody directed against CD52, can be administered through a peripheral vein and may have a cost advantage over other induction agents.[18] The IL-2R MAbs—daclizumab and basiliximab—are used interchangeably, although differences can exist between these two agents. Basiliximab is a chimeric antibody and retains the variable domains from the parent murine antibody; it has a higher affinity for the IL-2R than the fully humanized daclizumab.

POLYCLONAL ANTILYMPHOCYTE SERA

Polyclonal antilymphocyte agents are produced by immunizing animals with human lymphoid cells. In the case of Thymoglobulin, sera from rabbits immunized with human thymocytes are harvested and processed to obtain purified gamma globulin. The final product contains antibodies that react against a variety of targets, including red blood cells, neutrophils, dendritic cells, and platelets. Within hours of administration, polyclonal agents result in lymphocyte depletion secondary to a number of mechanisms, including complement-dependent and Fc-dependent opsonization and lysis. T and B lymphocyte counts can remain depressed up to 24 months after administration.[19] The polyclonal agents also contain antibodies to a wide variety of cell surface antigens, including the IL-2R adhesion molecles and costimulatory molecules.

Polyclonal agents are xenogeneic proteins and therefore elicit a number of side effects, including fever and chills. Less commonly, they can also induce a serum sickness like syndrome and, rarely, acute respiratory distress syndrome (ARDS).

Figure 35-1 demonstrates that the use of Thymoglobulin has been increasing to the point that it has become the most widely used induction agent in the United States.[4] This trend is likely on the basis of safety as compared to OKT3 (which has been associated with infusion-related side effects) and efficacy compared to its predecessor, ATGAM (a horse-derived polyclonal gamma globulin). In a prospective, double-blinded, randomized controlled study of Thymoglobulin versus ATGAM, Thymoglobulin induction was associated with a reduced incidence of acute rejection (4% vs. 25%, $p = 0.014$) and greater graft survival (98% vs. 83%, $p = 0.020$) at 1 year.[20] The salutary effects of Thymoglobulin induction on acute rejection incidence were persistent after 10 years of follow-up (11% vs. 42%, $P = 0.004$).[21] Although greater graft survival was observed with Thymoglobulin induction at 5 years compared to ATGAM,[22] this difference was not observed 10 years after transplantation.[21]

In a multicenter trial of induction therapy in deceased donor kidney transplant recipients considered to be at high risk for acute rejection or delayed graft function, Thymoglobulin induction in conjunction with cyclosporine-based maintenance immunosuppression was compared to the IL-2R MAb, basiliximab.[23] Although biopsy-proven acute rejection was less with Thymoglobulin induction compared to basiliximab (15.6 vs. 25.5%, $p = 0.02$), there was no difference in

patient or graft survival at 12 months.[23] Follow-up data on the 183 U.S. patients enrolled in the study revealed no difference in graft survival at 5 years.[24] There was no difference in the incidence of posttransplant lymphoproliferative disease (PTLD) and cancer between the two induction groups, and there was a slight increase in the rate of treated cytomegalovirus (CMV) infection in the basiliximab group.[24] Unfortunately, no information on long-term kidney function in these patients has been published. Although this study demonstrates a reduction in the incidence of acute rejection in patients receiving Thymoglobulin induction compared to basiliximab in cyclosporine-treated patients, it has not been adequately studied whether a similar effect on acute rejection would be observed in tacrolimus-treated patients.

ANTI-CD3 MONOCLONAL ANTIBODIES

OKT3 was approved in 1986 for the treatment of acute rejection. OKT3 is a murine IgG2 monoclonal antibody targeting the CD3 complex adjacent to the T-cell receptor. Soon after the injection of OKT3, T-cells disappear from circulation as a result of opsonization and removal from circulation by mononuclear cells in the liver and spleen. In addition, initially OKT3 can activate T-cells and result in the release of several cytokines, including IL-2, IFN-γ, IL-6, and tumor necrosis factor (TNF).[25] These cytokines cause a syndrome that has been referred to as the cytokine release syndrome and consists of fever, chills, headache, gastrointestinal complaints, and, less commonly, ARDS, aseptic meningitis, and encephalopathy. The availability of other induction agents and the severity of the side effects associated with the cytokine release syndrome have resulted in a marked reduction in the use of OKT3. Furthermore, OKT3 is immunogenic in humans, and approximately 50% of patients will make antibodies to it following a course of treatment.[26] Many of these patients will develop high-titer antimouse antibodies that preclude retreatment with OKT3. Currently, OKT3 is rarely used because of its side effect profile. There are several humanized nonactivating anti-CD3 MAbs that offer clear-cut advantages over the murine OKT3 but have yet to be developed for use in renal transplantation.

ANTI-CD52 MONOCLONAL ANTIBODIES

Alemtuzumab (Berlex Laboratories; Montville, New Jersey) is a humanized IgG1 monoclonal antibody directed against CD52, a glycoprotein present on circulating mononuclear cells. A rapid depletion of T and B lymphocytes, natural killer cells, and monocytes occurs within 1 hour after its administration, and reduced peripheral lymphocyte counts may persist beyond 1 year.[27] Although not FDA-approved for use in kidney transplantation, its use as an induction agent has become popular given its powerful depletional properties and favorable cost profile compared to other induction agents.

The early experience with alemtuzumab induction centered on creating a "prope," or near-tolerant state, by inducing perioperative lymphocyte depletion with alemtuzumab followed by low-dose cyclosporine monotherapy for maintenance immunosuppression.[28] Although short-term results were encouraging, 5-year follow-up data indicated that recipients on this protocol were susceptible to episodes of late rejection.[29] A pilot study of kidney transplant recipients on sirolimus monotherapy raised concerns for an increased risk for antibody-mediated rejection with alemtuzumab induction (cumulative incidence of antibody-mediated rejection 17%; follow-up 3–29 months),[30] although this observation may have resulted from inadequate maintenance immunosuppression. Using conventional triple immunosuppression with tacrolimus, mycophenolate mofetil (MMF), and prednisone, highly sensitized transplant recipients with either a positive cytotoxic or flow-cytometric crossmatch desensitized with intravenous immunoglobulin (IVIG) and/or rituximab had similar rates of acute cellular and antibody-mediated rejection with alemtuzumab induction as those induced with daclizumab or Thymoglobulin.[31–33] Steroid-free immunosuppression may be feasible in alemtuzumab recipients, although unacceptably high rejection rates were observed in kidney transplant recipients maintained on both CNI- and prednisone-free immunosuppression.[12] However, with tacrolimus-based steroid-free maintenance immunosuppression, comparable graft and rejection-free survival were observed in patients induced with alemtuzumab and IL-2RA MAbs.[15]

A potential concern with alemtuzumab therapy has been reports of an association with its use and the development of autoimmunity, particularly in the multiple sclerosis (MS) population. Approximately one-third of patients with MS treated with alemtuzumab developed Graves disease.[34] It has been suggested that autoimmunity develops in the setting of lymphopenia, where lymphocyte reconstitution and increased T-cell apoptosis and cell cycling are driven by elevated levels of IL-21.[35] A similar association with Graves disease has not been widely reported in the kidney transplant literature, although Kirk and colleagues did report one case of autoimmune thyroid disease developing in a kidney transplant recipient.[36] It is important to note that in both of these reports, a more intensive regimen of alemtuzumab was employed than that typically used for kidney transplant induction, and perhaps the higher dosing may be one contributing factor to the development of autoimmunity.

Long-term patient and graft outcomes with alemtuzumab induction are unclear, and only a few small studies have prospectively evaluated alemtuzumab induction with other induction agents.[37–39] Although initial costs of alemtuzumab induction therapy tends to be lower than that of other induction agents, a detailed cost analysis comparing induction agents has not been performed.

ANTI-IL2 RECEPTOR MONOCLONAL ANTIBODIES

The successful introduction of two MAbs—daclizumab (Zenapax, Roche Laboratories) and basiliximab (Simulect, Novartis Pharmaceuticals)—targeting the α-chain of the IL-2R can be attributed to the extensive investigative efforts performed on the IL-2R in the early 1980s.[40] The α-chain was the first of the three IL-2R subchains to be fully characterized and was initially identified as Tac (for T-cell activation) protein. The IL-2R β- and γ-chains are required to transduce the IL-2 signal inside the cell, while the addition of the α-chain leads to the expression of the high-affinity IL-2R. A MAb with the ability to block the interaction

between IL-2 and the α-chain of the high-affinity IL-2R-αβγ has the potential to block the amplification of the immune response and subsequent rejection. Promising clinical trials of murine or rat anti-IL-2R MAbs followed soon thereafter and were published in the late 1980s and early 1990s.[41,42] The chimerization and humanization of rodent antibodies resulted in more humanized constructs that had prolonged half-life and lacked immunogenicity. The phase III trials with daclizumab and basiliximab provided convincing and conclusive proof that blockade of the IL-2 pathway can result in significant reduction in acute rejection.[6–8]

The exact mechanism of action of the anti-CD25 MAbs is not completely understood. There is no evidence that long-term tolerance occurs with anti-CD25 MAb. Significant depletion of T-cells does not appear to play a major role in the mechanism of action of these MAbs. Studies with the anti-IL-2R MAbs suggest that the main mechanism of action of these antibodies is through saturation and blockade of the IL-2Rα subunit.[8,43] Saturation of the IL-2Rα subunit on circulating lymphocytes persists for up to 120 days after a course of daclizumab induction (1 mg/kg every 2 weeks for 5 doses), but higher-circulating concentrations (approximately 5 ug/ml) are required to block IL-2-mediated biological responses in vitro. These concentrations persist for about 70 days following a course of daclizumab induction. Basiliximab induction, when administered as a fixed dose of 20 mg given preoperatively and on day 4 after transplantation, results in IL-2Rα saturation on circulating lymphocytes for 25 to 35 days after transplantation.

Other mechanisms of action may mediate the effect of these antibodies. In a study of daclizumab-treated patients, there is approximately a 50% decrease in circulating lymphocytes staining with 7G7, a fluorescein-conjugated antibody that binds on the α-chain to an epitope distinct from the epitope that is recognized and bound by daclizumab.[8] Similar results were obtained by Amlot and colleagues in studies with basiliximab.[43] These findings indicate that therapy with the anti-IL-2R MAb results in a relative decrease of the expression of the α-chain either from depletion of coated lymphocytes and/or modulation of the α-chain secondary to decreased expression or increased shedding. There is also recent evidence that the β-chain may be downregulated by the anti-CD25 antibody.

At present, there is no marker or test to monitor the effectiveness of anti-IL-2R MAb therapy. Saturation of the α-chain on circulating lymphocytes, although important as a determinant of minimal blood concentrations, is not predictive of rejection that occurs during anti-IL-2R MAb therapy. Kovarik and colleagues analyzed the influence and duration of IL-2R blockade on the incidence of acute rejection episodes in patients who participated in the phase III basiliximab trials and who had detailed disposition analysis of basiliximab.[44] Duration of receptor blockade was similar in patients with rejection and without rejection (34 ± 14 days vs. 37 ± 14 days, mean + SD). In another daclizumab trial, patients with acute rejection were found to have circulating and intragraft lymphocytes with saturated IL-2R.[45] A possible explanation is that those patients who reject on anti-IL-2R blockade do so through a mechanism that bypasses the IL-2 pathway due to cytokine-cytokine receptor redundancy (i.e., IL-7, IL-15).

ANTI-CD20 MONOCLONAL ANTIBODIES

Whereas the preceding antibodies largely target the cellular immune response through binding of T lymphocyte epitopes, rituximab is a human-mouse chimeric MAb directed against the B lymphocyte receptor, CD20. It has been demonstrated to mediate B cell depletion through apoptosis in vitro and complement-dependent cell lysis and antibody-dependent cellular cytotoxicity in vivo. After the administration of a single dose, a rapid depletion of peripheral B-cells to 0%–2% of the total lymphocyte count ensues within two days.[46] B lymphocyte counts remain suppressed beyond 6 months after its administration.[47] Because of its action against B-cells, rituximab has been used in kidney transplantation to target the humoral pathway of the immune system.

Rixtuximab has been used for a variety of kidney transplant indications. It is perhaps most widely recognized for its role in desensitization protocols for ABO-incompatible (ABO-I) and positive crossmatch kidney transplants. The earliest use of rituximab for desensitization was as part of a preconditioning regimen consisting of a combination of plasmapheresis and/or immunoadsorption with or without IVIG and splenectomy.[48–50] Thereafter, subsequent series reported successful ABO-I and positive crossmatch transplants using rituximab without splenectomy.[51–53] As one would expect given the role of rituximab for pretransplant desensitization, B-cell ablative therapy with anti-CD20 MAb may also be used for the treatment of antibody-mediated rejection in conjunction with plasmapheresis and/or IVIG.[33,54]

Rituximab is also used for the management of PTLD. The rationale for its use stems from experience using anti-CD20 MAb for the treatment of various CD20-positive hematological malignancies.[55,56] Given that the majority of PTLD cases are of B-cell origin and express CD20, the use of rituximab for the treatment of PTLD, generally given at a dose of 375 mg/m^2 for four weekly infusions in conjunction with reduction of maintenance immunosuppression, has been used with some success.[57–59]

The use of rituximab for the treatment of both native and transplant glomerular diseases has been described. Reports of complete or partial remission of proteinuria have been published with the use of rituximab for native kidney glomerulopathies, such as membranous nephropathy, mixed essential cryoglobulinemia associated with hepatitis C, lupus nephritis, and ANCA-associated vasculitis.[60–64] These glomerulopathies are presumed to arise from deposition of circulating immunoglobulins or immune complexes onto the glomerular basement membrane, thus providing the rationale for the use of B-cell ablative therapy for treatment of these disorders. Limited data also exists for the use of rituximab for post-transplant glomerular diseases. A few case series have been published documenting the use of anti-CD20 therapy for recurrent membranous nephropathy in kidney transplant patients.[65,66] In one case report, complete remission of proteinuria ensued in a patient in whom an allograft biopsy revealed infiltrating CD20$^+$ lymphocytes in addition to the histological features of membranous nephropathy.[66]

Rituximab has also been used for posttransplant recurrent focal segmental glomerulosclerosis (FSGS) with mixed results. The pathogenesis of recurrent FSGS in kidney

transplant is suspected to be related in part to a circulating permeability factor that initiates glomerular injury.[67] It is postulated that rituximab therapy may exert its effects in recurrent FSGS by eliminating B-cells, thereby limiting the production of the circulating factor. An area of investigation includes the role of CD80, a transmembrane protein expressed on the surface of B-cells and other antigen-presenting cells, in modifying glomerular permeability.[68]

A case report identified infiltrating interstitial $CD20^+$ lymphocytes in a patient with recurrent FSGS recalcitrant to plasmapheresis.[69] After the administration of two doses of rituximab 375 mg/m^2, the patient had sustained remission of proteinuria 12 months later. However, Yabu and colleagues reported on four consecutive patients with early recurrence of FSGS unresponsive to plasmapheresis who continued to have nephrotic-range proteinuria despite the administration of two to six weekly infusions of rituximab 375 mg/m^2.[70] It is likely that heterogeneous factors contribute to the pathogenesis of recurrent FSGS. The variable response to anti-CD20 therapy in nephrotic patients with recurrent FSGS suggests that additional nonimmune factors are likely involved in the pathogenesis of recurrent FSGS.

BIOLOGICAL AGENTS IN DRUG MINIMIZATION TRIALS

As mentioned earlier, induction with biological agents has been used predominately to enhance the effectiveness of immunosuppression during the early transplant period, when the risk of acute rejection is the highest. As acute rejection rates have fallen over the years, there is now growing emphasis on minimizing the toxicities associated with maintenance immunosuppressive agents. Two major drug minimization paradigms exist: CNI-minimization and corticosteroid-minimization.

The nephrotoxic effects of CNIs have been well-described. Histological features include arteriolar hyalinosis, glomerulosclerosis, and focal areas of interstitial fibrosis and tubular atrophy (striped interstitial fibrosis), and can be seen as early as the first posttransplant month.[71] Furthermore, other side effects of CNIs include glucose intolerance, electrolyte disturbances (hyperuricemia, hypomagnesemia, hyperkalemia, metabolic acidosis), cosmetic changes (gingival hyperplasia, hirsutism, alopecia), neurotoxicity (tremors, seizures), hypertension, and dyslipidemia. Thus, trials have been conducted to examine the impact of CNI-free immunosuppression in an effort to avoid both nephrotoxic and extrarenal side effects.

In a multicenter trial of CNI avoidance, 98 *de novo* kidney transplant patients received daclizumab induction and maintenance immunosuppression with MMF and corticosteroids. Biopsy-proven rejection was quite high, occurring in 48% of patients at 6 months.[45] Therefore, subsequent randomized controlled CNI-avoidance trials have used sirolimus in place of CNI in combination with MMF and corticosteroids.[13,72] In each of these trials, antibody induction therapy with either IL-2 MAb or Thymoglobulin was administered. Although each of these sirolimus-based studies suggested that outcomes associated with CNI-free immunosuppression are comparable to CNI-based protocols, the small sample sizes in each study limit the statistical power to draw meaningful conclusions.

The SYMPHONY trial was a large prospective trial that was adequately powered to address the issue of whether induction therapy with an IL-2R MAb could facilitate low-dose maintenance immunosuppression in kidney transplantation.[73] Operating under the hypothesis that reduced exposure to CNI would yield less nephrotoxicity and consequently result in better renal allograft function, this multicenter international trial showed that patients receiving daclizumab induction and then maintained on low-dose tacrolimus, MMF, and corticosteroids had a higher estimated glomerular filtration rate (GFR) at 12 months, a lower rate of acute rejection, and better graft survival compared to standard-dose cyclosporine, MMF, and corticosteroids without antibody induction.[73] Furthermore, estimated GFR, incidence of acute rejection, and graft survival were better in the low-dose tacrolimus group compared to a group that received CNI-free immunosuppression with daclizumab induction, low-dose sirolimus, MMF, and corticosteroids.[73] This study suggests that induction therapy with IL-2R MAb may be used to facilitate low-dose CNI-based immunosuppression, particularly with tacrolimus. Also, it appears that low-dose sirolimus-based, CNI-free immunosuppression yields inferior short-term graft outcomes compared to low-dose CNI-based maintenance immunosuppression. However, this study does not answer how a maintenance regimen of full-dose sirolimus, MMF, and corticosteroids would fare in comparison to a low-dose CNI-based immunosuppression regimen nor does it assess whether the favorable graft outcomes seen with low-dose CNI would still be observed if daclizumab induction was used with standard-dose cyclosporine.

A considerable degree of attention has centered on corticosteroid-minimization immunosuppression protocols to reduce the toxicity of prolonged steroid exposure. Two main strategies exist for steroid-minimization, both of which rely on the use of induction therapy with biological agents: complete steroid avoidance and early steroid withdrawal. Matas and colleagues used Thymoglobulin induction and early steroid withdrawal on postoperative day 6 in conjunction with one of three maintenance immunosuppression regimens: cyclosporine and MMF, low-dose tacrolimus and standard-dose sirolimus, or standard-dose tacrolimus and low-dose sirolimus. In mostly low-immunological risk patients, actuarial patient and allograft survivals at 5 years were 91% and 84%, respectively, and rejection-free survivals at 48 months were 86% in living donor and 80% in deceased-donor recipients. Although excellent long-term graft outcomes were reported in this study, it is important to note that this series was uncontrolled and that only 27 of the original 589 patients remained in the analysis at 5 years. Therefore, it is difficult to draw conclusions about long-term graft outcomes associated with steroid minimization from this single-center experience, and these findings may not be generalizable to other populations.

The FREEDOM study was a noninferiority trial comparing complete steroid avoidance, early steroid withdrawal on posttransplant day 7, and standard corticosteroid doses.[74] Patients in each study arm received basiliximab induction and were maintained on cyclosporine and enteric-coated mycophenolate sodium. In this study, the median difference in GFR at 12 months for patients in either steroid-free group compared to standard steroids did not meet the prespecified noninferiority margin in the intent-to-treat analysis. Although noninferiority was achieved in the analysis of

observed cases, 41% of patients in the steroid avoidance arm and 29% in the early steroid withdrawal group were started on steroids before the end of the study period. Furthermore, the 12-month incidence of biopsy-proven acute rejection was significantly higher in the steroid avoidance group compared to standard steroids (29.6% vs. 19.3%, $p = 0.007$). Thus, this short-term study suggests that steroid minimization in IL-2 MAb treated patients in conjunction with a cyclosporine-based maintenance immunosuppression regimen may lead to worsened graft function compared to those maintained on standard maintenance steroids.

Woodle and colleagues explored the issue of whether early corticosteroid withdrawal at 7 days posttransplant is comparable to chronic steroid therapy in kidney transplantation with a maintenance regimen of tacrolimus and MMF in a multicenter double-blinded, randomized controlled trial.[75] The choice of induction agent was at the discretion of individual transplant centers participating in this trial. Roughly two-thirds of the participants received Thymoglobulin induction, while the remaining received IL-2 MAb induction with either basiliximab or daclizumab. After 5 years of follow-up, there was no difference between the two groups in patient survival, graft survival, biopsy-proven acute rejection rates, and renal function. Patients in the corticosteroid withdrawal group had improved serum triglycerides and less severe diabetes.[75]

A concerning issue from Woodle's study was an observation from posthoc analysis of a higher incidence of chronic allograft nephropathy on biopsies performed for-cause in patients from the corticosteroid withdrawal group.[75] Because protocol biopsies were not done in this study, it is unknown whether this is a finding that is generalizable to all patients maintained without corticosteroids. A smaller prospective study conducted by Laftavi and colleagues found a trend toward greater chronic fibrosis scores at 1 year on protocol biopsies in patients who had steroids discontinued at day 7 posttransplant compared to those maintained on chronic corticosteroids.[76] Larger long-term studies using protocol biopsies at prespecified time points are needed to establish the safety of steroid minimization in kidney transplantation.

In summary, although there is concern regarding toxicity associated with each of the immunosuppressive agents currently in use in kidney transplantation, the risk/benefit ratio of drug minimization remains unsettled, and larger long-term studies are awaited to establish the benefit of immunosuppression minimization.

EMERGING BIOLOGICAL AGENTS

An alternative approach to drug minimization is the use of biological agents for maintenance immunosuppression. Biological agents currently under investigation for use as maintenance immunosuppression include costimulatory blockers and antiadhesion molecules. Other attractive targets for immunosuppression include the use of complement inhibitors.

COSTIMULATORY BLOCKADE

Costimulation, also known as signal 2 in the T-cell activation pathway, has attracted considerable interest as a target for immunosuppression. In experimental models, T-cell receptor stimulation by antigen bound to major histocompatibility complex (MHC) from an antigen-presenting cell in the presence of costimulatory blockade results in antigen-specific unresponsiveness, or anergy.[77] Several costimulatory molecules have been the subject of investigation, but only abatacept, a fusion protein of the extracellular portion of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) with the constant-region fragment (Fc) of human IgG1, has gained approval for clinical use. Abatacept acts as a competitive antagonist of CD28 for binding of CD80/86 on the antigen-presenting cell surface and is used for the treatment of rheumatoid arthritis. Belatacept (LEA29y), a second-generation analogue of abatacept, has greater affinity to CD80 and CD86 and is a more potent inhibitor of T-cell activation. Results of a phase II clinical trial in kidney transplantation comparing two dosing regimens of belatacept against cyclosporine were reported in 2005.[78] When used in conjunction with basiliximab induction, MMF, and corticosteroids, the two dosing regimens of belatacept were not inferior to cyclosporine for the primary efficacy endpoint of cumulative incidence of biopsy-proven acute rejection at 6 months. Furthermore, GFR measured by iohexol clearance at 12 months was significantly higher in belatacept-treated patients compared to those receiving cyclosporine.

Patients from the phase II and III belatacept trials were studied for the effect of belatacept and IL-2R MAbs on T-regulatory cells.[79] Whereas belatacept had no effect on circulating T-regulatory cell numbers, anti-CD25 therapy with basiliximab resulted in a profound reduction in $CD4^+CD25^+FOXP3^+$ T-regulatory cells within 7 days of treatment with recovery by 90 days posttransplant.[79] The clinical implication of this effect is unclear, as there appeared to be an associated decrease in potential allograft-specific effector T-cells and an increase in the percentage of $CD25^-FOXP3^+$ T-regulatory cells over time.[79]

Two separate phase III trials have now been completed with dosing modifications to belatacept that are intermediate in intensity compared to the two dosing regimens used in the phase II trial: belatacept in a more intensive and less intensive regimen versus cyclosporine in conjunction with basiliximab induction, MMF, and corticosteroids in 1) standard criteria deceased donor kidneys and living donor kidney transplants (the BENEFIT study), and 2) extended criteria donor kidney transplants (BENEFIT-EXT). Additionally, a CNI conversion to belatacept trial and a steroid withdrawal trial using maintenance immunosuppression with belatacept and either MMF or sirolimus are currently ongoing. Results from BENEFIT and BENEFIT-EXT were reported at the American Transplant Congress in 2009.[80,81] In the BENEFIT study, acute rejection was higher in the belatacept arms compared to cyclosporine (22% with more intensive belatacept, 17% with less intensive belatacept, 7% with cyclosporine; less-intensive belatacept was noninferior to cyclosporine), but patient and graft survival were noninferior with both regimens of belatacept at 12 months compared to cyclosporine.[80] Moreover, the composite renal endpoint of measured GFR by iohexol clearance at 12 months of less than 60 ml/min/1.73 m^2 or a decrease in measured GFR of greater than 10 ml/min/1.73 m^2 from month 3 to month 12 was less frequent in both belatacept arms compared to cyclosporine, suggesting superior renal function in those treated with belatacept (55% more intensive; 54% less

intensive; 78% cyclosporine; $p < 0.0001$ more intensive or less intensive vs. cyclosporine).[80] Similarly, BENEFIT-EXT showed similar patient and graft survival with more intensive and less intensive belatacept compared to cyclosporine, but unlike BENEFIT, there was no difference in acute rejection rates between both belatacept arms and cyclosporine in BENEFIT-EXT (17% more intensive, 18% less intensive, 14% cyclosporine).[81]

Superior renal function was also observed in both belatacept arms in BENEFIT-EXT compared to cyclosporine, with 71% of more intensive and 76% of less intensive belatacept reaching the composite renal endpoint compared to 85% in cyclosporine-treated patients ($p = 0.002$ more intensive vs. cyclosporine; $p = 0.06$ less intensive vs. cyclosporine).[81] Thus, the phase III trials suggest that the less intensive regimen may be preferable to the more intensive regimen. Of note, in the BENEFIT trial, there were three cases of PTLD reported in patients treated with the more intensive belatacept dosing regimen and two cases in the less intensive belatacept group compared to one case in the cyclosporine group. The greatest risk for PTLD seemed to be in those patients who were EBV negative and/or received depleting agents.

ANTIADHESION MOLECULES

The leukocyte function associated antigen 1 (LFA-1) is a member of the heterodimeric B2 integrin family and consists of a noncovalently linked unique alpha chain (CD11a) and a beta chain (CD18). It primary interaction is with ICAM-1, but it also interacts with ICAM-2 and ICAM-3. Its function as an adhesion molecule is important for transendothelial migration of leukocytes to the site of injury. Other data suggest that LFA-1 serves to strengthen the avidity of T-cell and antigen-presenting cell binding[82] and may provide costimulatory signals to resting T-cells.[83] These events are important for early T-cell activation. Furthermore, LFA-1 is also present on B-cells, and its interaction with ICAM-1 may enhance B-cell antigen presentation.[84]

Efalizumab is a humanized IgG1 murine anti-CD11a monoclonal antibody that was approved by the FDA in 2003 for the treatment of chronic moderate-to-severe plaque psoriasis as a once-weekly subcutaneous injection. Its use in kidney transplantation was evaluated in a phase I/II trial using two separate doses (2 and 0.5 mg/kg) in conjunction with half-dose cyclosporine, sirolimus, and prednisone or full-dose cyclosporine, MMF, and prednisone.[85] Study subjects received weekly efalizumab injections for 12 consecutive weeks, and protocol kidney biopsies were performed at 3 months. Biopsy-proven acute rejection rates at 6 months were low across the entire study cohort (four of 38 patients, 11%). An additional two patients had mild subclinical acute rejection (Banff grade 1A). Saturation of the CD11a binding sites was equivalent with both doses of efalizumab and was sustained beyond the completion of the treatment course as evidenced by mean available binding sites returning to pretreatment levels 3 months after the last administration of efalizumab.

Of note, three cases of PTLD developed among patients given the higher dose of efalizumab in conjunction with full-dose cyclosporine, MMF, and prednisone. Furthering the safety concerns regarding efalizumab were FDA-issued warnings in October 2008 of an increased incidence of progressive multifocal leukoencophalopathy, bacterial sepsis, viral meningitis, and invasive fungal disease in response to postmarketing surveillance of patients receiving efalizumab for the treatment of psoriasis. As a result, efalizumab has been withdrawn from the market, and clinical trials using efalizumab have been discontinued.

Alefacept is a human LFA-3-IgG1 fusion protein that binds to CD2 on T-cells, thereby interfering with T-cell activation. It is FDA-approved for the treatment of moderate-to-severe chronic plaque psoriasis. Treatment with alefacept results in a selective reduction in T-effector memory cells and spares naïve T-cells.[86] Currently, a phase II clinical trial is underway investigating the use of alefacept for kidney transplantation.

COMPLEMENT INHIBITION

In antibody-mediated rejection, the classical pathway of the complement cascade is triggered by donor-specific antibody binding to allograft endothelium, thus exposing a binding site on the antibody for C1. This initiates a cascade of events that leads to the formation of C5 convertase, which cleaves C5 into C5a and C5b. C5b, in turn, binds C6-9 to form the membrane attack complex (C5b-9), which ultimately leads to target cell lysis. Eculizumab (Alexion, Cheshire, Connecticut) is a humanized anticomplement C5 antibody that inhibits cleavage of C5 to C5a and C5b, thus preventing complement-dependent cytotoxicity.[87]

Given its role in blocking antibody-mediated effector responses, eculizumab would be a logical therapeutic agent for the treatment of antibody-mediated rejection. Locke and colleagues reported on the compassionate use of eculizumab as rescue therapy for a patient with severe antibody-mediated rejection refractory to treatment with plasmapheresis followed by low-dose IVIG.[88] After the administration of eculizumab 600 mg intravenously, the patient had clinical and histological improvement of antibody-mediated rejection. Furthermore, there was a reduction in C5b-9 staining within the interstitium, blood vessels, and tubular basement membranes observed in histological samples taken after eculizumab administration. Thus, complement inhibition is an attractive target for the treatment and/or prevention of antibody-mediated rejection, but experience using eculizumab is limited, and larger series are needed to establish its safety and efficacy in kidney transplantation.

SUMMARY

Biological agents, mainly in the form of induction therapy, are used in the majority of kidney transplant patients to decrease the risk of acute rejection in the early transplant period. Newer biological agents are currently in development for use in maintenance immunosuppression and for the treatment of transplant glomerulopathies and acute rejection. Novel targets for immunosuppression have been discovered, and biological agents are likely to represent an important component of our immunosuppressive repertoire.

A full list of references are available at www.expertconsult.com.

Chapter 36

CURRENT AND EMERGING MAINTENANCE IMMUNOSUPPRESSIVE THERAPY

Simin Goral, M.D., and J. Harold Helderman, M.D.

This chapter reviews current immunosuppressive management in kidney transplantation and emphasizes the emerging features that have led to a more individualized approach to each patient. The dictum of accommodation between host and graft drives the construction of unique immunosuppressive management strategies in transplantation. It has been observed that the technical and immunological graft loss rates are highest within the first several months after engraftment. After the first year, graft loss rates become nearly linear over time, permitting construction of graft half-life curves with high confidence.[1] Corollary to the law of graft half-life accommodation is the rule that heightened immunosuppression is required early, with progressive reduction in the amount and stringency over time. Until highly allospecific immunity or tolerance can be achieved, this strategy of "more early and less late" will continue to define the role of immunosuppression, regardless of the agents employed. Efforts to find new agents will also continue as long as we strive for better long-term patient and graft survival. Current research is focused not only on decreasing drug-related side effects but also on preventing subclinical rejection, chronic antibody-mediated rejection, and chronic allograft nephropathy, and reducing costs and increasing compliance in transplant recipients.

Pursuant to the dictum of accommodation, three distinct periods of transplantation immunosuppression have been defined:

1. The perioperative induction period
2. Early maintenance, characterized by progressive taper of the individual drugs in the regimen
3. Chronic maintenance, characterized by a relatively fixed package of agents used at the lowest effective doses until an intervening event occurs, such as late acute rejection, infection, or neoplasm

We also discuss induction therapy briefly in this chapter, and the agents used in the early- and late-maintenance phases of immunosuppression. Since they are similar, they are discussed together.

INDUCTION IMMUNOSUPPRESSION

In the perioperative period, steroids are given initially at high doses; rapid tapering is then instituted to achieve the levels used in the early-maintenance phase. The rapidity of the tapering varies from center to center. Usually, the patient receives a 250-mg to 500-mg pulse of intravenous (IV) methylprednisolone during surgery. Antiproliferative agents such as azathioprine or mycophenolic acid (MPA) are frequently used at the same time. Azathioprine is typically given as an intravenous dose of 3 to 5 mg/kg, followed by a rapid taper to the induction dose of 150 mg/day for 5 days and leading into the early maintenance dose of 100 mg/day or 2 mg/kg/day, whichever is lower, adjusted by marrow toxicity. Initial doses of MPA are typically 720 to 1440 mg/day for enteric-coated mycophenolate sodium and 1 to 3 g/day for mycophenolate mofetil in divided doses.

The greatest differences in induction strategies involve 1) whether or not to use a calcineurin inhibitor (CNI) such as cyclosporine (CsA) or tacrolimus (TAC) or 2) whether or not to provide a T-cell-directed polyclonal or monoclonal antibody for a defined period before introducing the CNI to enter the early-maintenance phase of immunosuppression. The development of the *antibody-induction approach* stemmed from the recognition that cyclosporine and tacrolimus are nephrotoxic, thus potentially compromising early graft function.

A sequential induction approach, which was developed to avoid early CsA use, employs anti-T-cell antibodies that are

extraordinarily effective at forestalling acute rejection when used early.[2] A short overlap period follows, during which CNI is introduced. The achievement of target blood levels of CNIs is determined empirically at rejection prophylaxis.[3] When these target levels are achieved, the antibody is discontinued, the induction phase is considered complete, and the recipient enters the early-maintenance phase of immunosuppression. Testing the role of antibody induction requires carefully constructed, large trials (which have been rare) or an approach to the data that employs statistical tools of metaanalysis. According to OPTN/SRTR data base, in recent years, there has been an increasing trend toward the use of induction therapy with antibodies.[4] Shield and colleagues[5] analyzed the large United Network for Organ Sharing (UNOS) database and demonstrated improved outcomes with the use of antilymphocyte preparations, both Minnesota antilymphocyte globulin and OKT3, during the early posttransplant period. In another study, Szczech and colleagues[6] looked at the combined individual patient-level data from published trials to examine the effect of induction therapy on allograft survival. They showed a benefit of induction therapy at 2 years, particularly among presensitized patients. Although the benefit of this therapy subsequently waned, presensitized patients continued to have benefit at 5 years. On the other hand, Meier-Kriesche and colleagues[7] demonstrated in 73,707 patient using registry data that antilymphocyte antibody induction therapy was significantly associated with early death due to infection and cardiovascular causes, in addition to significant risk for long-term malignancy-related death.

Currently, in contrast to sequential induction approach, using overlap with maintanenance agents, short courses of potent new anti–T lymphocyte antibodies are being used. Induction antibodies, especially the newer ones such as interleukin-2 (IL-2) receptor antibodies, antithymocyte globulin, and alemtuzumab, and the risks of their use are discussed in more detail in Chapter 35.

THE MAINTENANCE PHASE

Therapeutic Approach

Following the accommodation dictum, the transplant recipient enters early and then late maintenance with progressive graft survival. In the following section, we review each agent used for immunosuppressive maintenance individually, with a focus on newer approaches. It is appropriate to first provide a general framework for the therapeutic approach in these next two immunosuppressive periods.

The bedrock of maintenance immunosuppression since the early 1980s has been a CNI with some form of adjunctive immunosuppression. In most programs, steroids were added as a second immunosuppressive drug ("double therapy"), or a cytotoxic agent was also used ("triple therapy"). Azathioprine was the predominant cytotoxic agent used until the early 1990s, when it was superseded in most programs by mycophenolate mofetil (MMF), based on evidence from three large randomized, prospective, blinded cooperative treatment trials conducted worldwide.[8] No clear graft survival advantage has been shown with azathioprine-based triple therapy over double therapy.[9,10] The important reduction in early acute rejection rates with MMF-based triple therapy drives the popularity of that regimen.

Immunosuppressive Agents

Steroids

Although not an emerging maintenance therapeutic agent, steroids remain a basic element in many protocols; thus, a brief discussion of standard uses and attempts at steroid withdrawal is in order. Corticosteroids have been used for prevention as well as for treatment of acute allograft rejection since the early 1960s. They block the expression of several cytokine genes and the synthesis and action of several chemoattractants and vasodilators as part of their antiinflammatory properties. In some transplantation centers, steroids are administered in the perioperative period as part of induction therapy (e.g., methylprednisolone, 250–500 mg, given intravenously), followed by prednisone, 30 mg/day in two or three separate doses. The dose is gradually tapered over 1-3 months to a maintenance dose of 5–10 mg daily.

The long-term use of steroids causes numerous and diverse complications, including growth retardation in children, osteoporosis, avascular necrosis, hyperlipidemia, hypertension, cataracts, and diabetes. To minimize or eliminate the occurrence of these complications, studies have been undertaken and are in progress at a number of transplantation centers. The potential benefits of eliminating steroids from the immunosuppressive regimens must be weighed against the risk of acute or chronic rejection and eventually early loss of the allograft. A metaanalysis by Hricik and colleagues[11] suggested that the elimination of steroids is associated with an increased short-term risk of acute rejection, with no statistically significant adverse effect on long-term patient or allograft survival in patients treated with a cyclosporine-based immunosuppressive regimen. These studies, however, had a great deal of heterogeneity in their designs and outcomes and short follow-up periods. Moreover, the experience of the Canadian Multicentre Transplant Study Group[12] with steroid withdrawal revealed that statistically significant differences in outcomes could be seen only after prolonged follow-up (more than 3 years), raising caution and potentially explaining the results of the Hricik study.

Two randomized trials studied the potential risks and the benefits of late steroid withdrawal (3 months after transplantation) while patients are on cyclosporine and MMF.[13,14] The investigators concluded that for recipients on cyclosporine, MMF, prednisone with no acute rejection at 90 days, the chance of developing subse-quent acute rejection is small. When prednisone was tapered and withdrawn, the risk of acute rejection increased, but withdrawal patients had a lower cholesterol level, less need for antihypertensives, and increased lumbar spine bone density. Of note, acute rejection risk was higher in blacks (39.6%) versus nonblacks (16%). Pascual and colleagues[15] performed a metaanalysis of randomized controlled studies of steroid avoidance or withdrawal providing that one treatment arm consisted in steroid avoidance or withdrawal and intention-to-treat rates of acute rejection and graft failure were clearly established after steroid avoidance or use or withdrawal or continuation.

They included 30 studies (5949 participants) and demonstrated that steroid-sparing strategies showed no effect on mortality or graft loss, including death. Patients on any steroid-sparing strategy showed a higher risk of graft loss excluding death than those with conventional steroid use, especially in those not receiving MPA or everolimus. But most notably, acute rejection was more frequent with a steroid-sparing strategy and more frequent after steroid withdrawal or avoidance when compared with standard steroid treatment when CsA was used.

A recent randomized, double-blind, placebo-controlled trial of early steroid withdrawal (at 7 days posttransplant) in 386 patients demonstrated an increase in biopsy-confirmed acute rejection primarily because of mild, Banff 1A, steroid-sensitive rejection, yet similar long-term (5-year follow-up) renal allograft survival and function.[16] The majority of patients received induction therapy, mostly with antithymocyte globulin. Weight change over time favored steroid withdrawal expressed as median change from baseline at 5 years—5.1 versus 7.7 kg, $p = 0.05$—yet interestingly no differences were observed in mean weight change between groups.

Although they did not perform pretransplant or posttransplant protocol biopsies, in posthoc analysis, a 5.8% increase in chronic allograft nephropathy (CAN) was noted in the steroid withdrawal group through 5 years (9.9% vs. 4.1%; $p = 0.028$). Although there are many theoretical and practical benefits of withdrawing steroids from the maintenance immunosuppressive regimens, we believe that clinicians should be cautious when considering steroid minimization because of the unresolved issues such as the timing of steroid discontinuation, infrequent use of controls in most of the trials, concerns over the lack of long-term follow-up and the effects of increased risk of CAN on long-term graft function and survival, and the other immunosuppressive drugs included in the protocol, allowing the safest steroid minimization protocol.

Cyclosporine

Before the discovery of the antirejection properties of CsA, the graft and patient survival rates after kidney transplantation were barely acceptable, and transplantation of other solid organs remained highly experimental. The introduction of cyclosporin A into the clinical arena of transplantation in 1978 revolutionized medical management after transplantation and improved early graft survival significantly. Because of its profound impact on transplantation, a CsA-based immunosuppressive regimen had become the gold standard of maintenance immunosuppression.

CsA is a small polypeptide of fungal origin. It binds to cyclophilin, a cytoplasmic receptor protein, and creates an active complex. By binding to calcineurin, a calcium-regulated enzyme, the cyclosporine-cyclophilin complex inhibits the expression of several critical T-cell activation gene transcription factors, thus forestalling the activation and proliferation of lymphocytes (Figure 36-1). The form of this drug that was initially available, Sandimmune, has pharmacokinetic properties that have made it difficult to use. There is a great deal of interpatient and intrapatient variability in exposure to the drug with standard dosing, whereas 12-hour trough blood levels are poorly reflective of drug exposure.

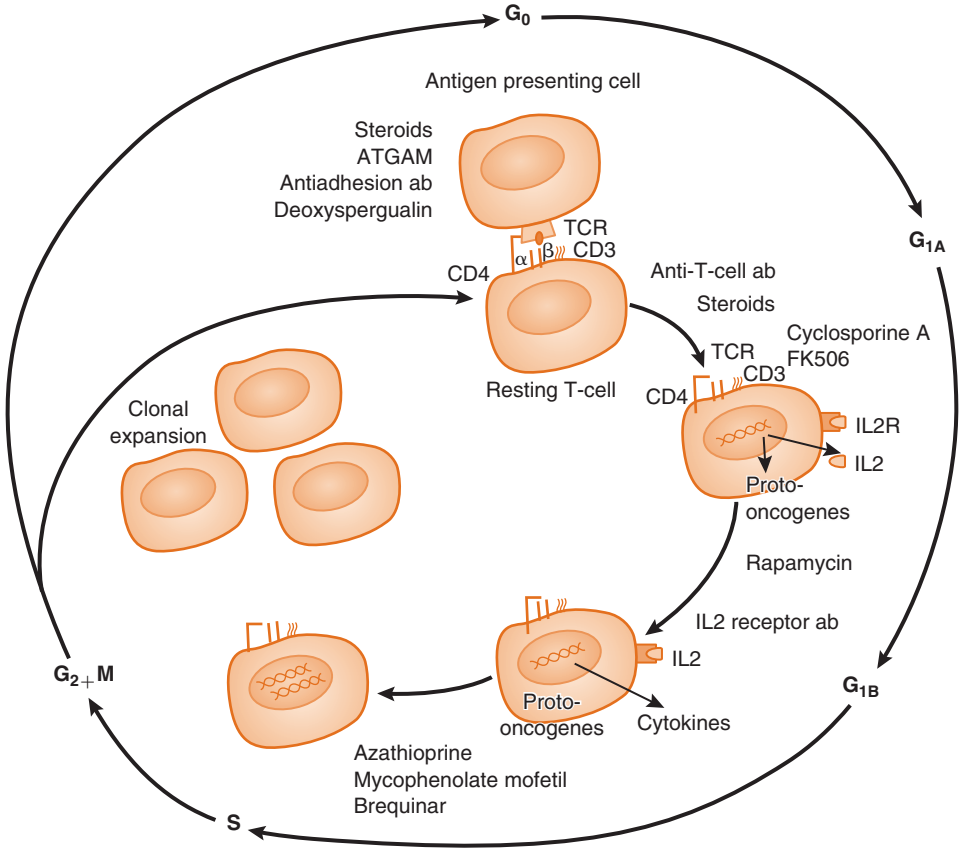


FIGURE 36-1 Lymphocyte activation cascade, with mechanism of actions of various immunosuppressive agents. *ab,* Antibody; *ATGAM,* antithymocyte globulin; *IL2,* interleukin-2; *TCR,* T-cell receptor.

Both gut motility and bile are required for adequate gastrointestinal absorption. Certain groups of patients (e.g., children, African Americans, and diabetic patients) absorb drugs poorly and are thus vulnerable to rejection.

A microemulsion formulation of CsA, *Neoral*, entered the clinical arena of transplantation in 1995. This formulation is a preconcentrate that, on contact with gastrointestinal fluids, rapidly forms a microemulsion, resulting in increased absorption of cyclosporine that is unaffected by food intake or the presence of bile. Neoral has shown increased bioavailability and decreased intrapatient and interpatient variability. The area under the curve (AUC) 0 to 4 hours represents the period of greatest variability among transplant recipients. Adequate absorption is very important for effective rejection prophylaxis. It has been shown previously that although the correlation between cyclosporine trough blood concentrations and total systemic exposure measured by the AUC is improved with Neoral, the C0 trough level does not correlate well with AUC.[17,18]

Recent studies indicated that a 2-hour postdose sample, C2, is the best single time-point predictor of AUC 0 to 4 in all solid organ transplants.[19,20] Dose reduction, depending on the C2 levels in many overexposed patients, may lead to improvements in renal function and blood pressure and a decrease in the incidence of chronic allograft nephropathy as well. Further studies are required to confirm the long-term benefits of this strategy. Replication of these studies in patient groups with different absorptive characteristics such as children and diabetics with gastroparesis would also be necessary.

No significant difference has been demonstrated in safety and tolerability between the standard oil-based cyclosporine (Sandimmune) and the new formulation.[21] The absorption of CsA has been markedly improved by conversion of even stable patients from Sandimmune to Neoral, especially poor absorbers, such as diabetic recipients of simultaneous kidney and pancreas allografts.[22] Indeed, a metaanalysis of a global database of worldwide studies of conversion showed the most dramatic improvement in the worst absorbers.[23] Finally, Kahan and colleagues[24] revealed an association between variable oral bioavailability of cyclosporine and risk of chronic rejection, which theoretically can be reduced by switching patients from Sandimmune to Neoral.

New patients are started on Neoral at a dose similar to that of Sandimmune, with adjustments in dosing made to achieve the same target blood levels. In several studies, 1:1 dosage conversion from Sandimmune to Neoral was safe for most stable patients.[25,26] However, it is strongly recommended that serum creatinine and cyclosporine blood levels be closely monitored, with the first time point at 7 days after conversion, to capture any cyclosporine-related toxic events because a 10% to 20% dose reduction is frequently required. Neoral is available in the same oral dosage strengths and forms as Sandimmune (25 and 100 mg, capsules, and 100 mg/ml, oral solution).

Table 36-1 reviews the toxicity profile of cyclosporine. Similar adverse effects have been reported with Neoral. Long-term studies should help determine whether the improved bioavailability and higher peak concentrations of Neoral will lead to reduced chronic rejection and longer graft survival or to increased chronic nephrotoxicity.

TABLE 36-1 Potential Adverse Effects of Cyclosporine

Nephrotoxicity
Hypertension
Hyperkalemia
Hypomagnesemia
Hyperuricemia
Thromboembolic events
Hepatotoxicity
Thrombotic microangiopathy
Hypertrichosis
Gingival hyperplasia
Hyperlipidemia
Glucose intolerance
Neurotoxicity
Chronic renal interstitial fibrosis
BK virus nephropathy

Another major development in transplantation therapeutics involving the cyclosporine molecule is the advent of generic formulations for study; these triggered discussion even before market availability. The type of the generic formulations (the old formulation of cyclosporine versus the newer microemulsion), their success in clinical trials, and their cost will have a major impact on their future use. Using an open-label, three-period design, Roza and colleagues[27] studied 50 renal transplant recipients taking stable doses of Neoral. Subjects switched from Neoral on a milligram-for-milligram basis to Gengraf. The pharmacokinetics of Gengraf were equivalent and indistinguishable from those of Neoral. Gengraf was well-tolerated and interchangeable with Neoral in these stable renal transplant recipients.

To gain wide acceptance in the transplantation community, the generic cyclosporine formulations must be held to a higher standard than is usually applied by the U.S. Food and Drug Administration (FDA) censure of generic drugs. When the FDA approves generic substitution, it makes a reference that permits free institution of any generic. This approach might be quite dangerous in our patient population, since a generic may be chemically identical and is delivered to the site of action at the same rate and extent as the innovator molecule, but it may not be bioequivalent to another generic.[28] Rightly so, two consensus conferences from 2001 reported certain recommendations from the experts in transplantation: Any switch between CsA formulations in a particular patient should take place only in a controlled setting with adequate pharmacokinetic monitoring. Generic medications should be clearly labeled and distinguishable from innovator drugs, and patients should be educated to inform their physicians of any switch to or among generic alternatives. There was also strong support for studies in high-risk patients such as African Americans and children to demonstrate bioequivalence.[29,30]

In this medical arena, in which survival of the organ transplant is at stake, mere bioequivalence (within 30%) after single-dose comparisons in young, healthy volunteers is an inadequate criterion for acceptance. At the least, especially

because this molecule has a complex pharmacokinetic profile, different patient populations and perhaps even efficacy data should be the standards on which approval is based. Because of the significant long-term side effects of CNIs, including nephrotoxicity, cardiovascular diseases, and malignancy, there are new trials on the way to minimize the use of these agents. The introduction of newer and potent agents in recent years has prompted interest in CNI-sparing (the initial use of a standard or low-dose CNI with subsequent withdrawal) and CNI-avoidance (completely avoiding the use of CNI) protocols. The physicians should be aware that these strategies are not safe for all patients. The studies are in progress.

Tacrolimus

Tacrolimus (FK-506; Prograf) is an immunosuppressive agent that was approved by the FDA in 1994 for use in liver transplant recipients and in 1997 for use in kidney transplant recipients based on trials in which TAC was used either as the primary immunosuppressive agent or as rescue therapy in steroid-resistant rejection.[31,32] Tacrolimus is a macrolide antibiotic that was isolated in 1985 from a soil actinomycete. It blocks T-cell activation genes by a mechanism similar to that of cyclosporine (see Figure 36-1). By binding to a ubiquitous, highly conserved cytosolic protein (FK-506-binding protein [FKBP]), the class of which has been labeled the immunophilins, TAC blocks the activation of calcineurin, a calcium-activated serine-threonine phosphatase, and inhibits the calcium-dependent signal transduction pathway in T lymphocyte activation. In open-label phase III studies, acute early transplant rejection rates, antirejection medication use, and the histological severity of rejection were all reduced by TAC, as compared to Sandimmune.[33] In these trials, the toxicity profile favored cyclosporine. The target range of trough blood level that optimizes efficacy and minimizes toxicity appears to be 5 to 15 ng/ml. The corresponding recommended initial dose of TAC is 0.1 to 0.2 mg/kg/day.

The toxicity profile of TAC is similar to that of cyclosporine (Table 36-2). The characteristics of nephrotoxicity include new arteriolar hyalinosis, degeneration or necrosis of smooth muscle cells of the media of the afferent and efferent arteriolar walls, and vacuolization of the proximal tubule. Neurotoxicity and diabetes occur more frequently with TAC than with cyclosporine.

TABLE 36-2 Potential Adverse Effects of Tacrolimus

Nephrotoxicity
Neurotoxicity
Gastrointestinal disturbances
Diabetes
Thrombotic microangiopathy
Alopecia
Hypertension
BK virus nephropathy
Chronic renal interstitial fibrosis
Hyperkalemia
Hypomagnesemia

Although the pathogenesis of diabetes due to TAC is not well-understood, it has been reported that TAC decreases glucose-induced insulin release at high concentrations by decreasing insulin mRNA secretion and reducing insulin production, which can be reversible both in animals and also in humans. On the other hand, islet cell damage was studied in 26 pancreas allograft biopsies, which revealed cytoplasmic swelling and vacuolization, and a marked decrease or absence of dense-core secretory granules in beta cells on electron microscopy; the changes were more pronounced in patients on TAC versus CsA.[34]

The Diabetes Incidence after Renal Transplantation: Neoral C(2) Monitoring Versus Tacrolimus (DIRECT) study was an international prospective randomized controlled trial that compared the glycemic influence of cyclosporine and tacrolimus.[35] Treatment with tacrolimus was associated with a significant increased risk of new-onset diabetes and impaired fasting glucose at 6 months posttransplant, relatively short-term follow-up, and without any difference in efficacy between the two agents ($p = 0.046$).

Obesity, a family history of diabetes, a history of glucose intolerance, positive hepatitis C status, and the use of high steroid doses are some of the risk factors for diabetes in patients taking TAC. A retrospective study by First and colleagues[36] showed that the incidence of posttransplant diabetes mellitus (PTDM) was 4.9% in tacrolimus-treated patients compared to 3.3% in cyclosporine-treated patients ($p = 0.453$). In this particular study, the absence of an antiproliferative agent correlated with the development of PTDM. In another study, using data from the United States Renal Data System, Kasiske and colleagues[37] identified 11,659 Medicare beneficiaries who received their first kidney transplant from 1996 to 2000. The cumulative incidence of PTDM was 9.1%, 16%, and 24% at 3, 12, and 36 months posttransplant, respectively. Using Cox's proportional hazards analysis, they demonstrated that risk factors for PTDM included age, African American race, Hispanic ethnicity, male donor, increasing human leukocyte antigen (HLA) mismatches, hepatitis C infection, body mass index greater than or equal to 30 kg/m^2, and the use of tacrolimus as the initial maintenance immunosuppressive medication. Recently, there has been a trend for reduced requirement for maintenance steroid doses and lower target trough levels of tacrolimus. Therefore, these metaanalyses just mentioned might have overestimated the incidence of posttransplant diabetes in kidney transplant recipients. Tremors, headache, seizures, and insomnia are also reported with use of this drug. Diarrhea, nausea, and anorexia are relatively common in patients receiving TAC. The incidences of hyperlipidemia and hypertension are lower with TAC than with cyclosporine. Gloor and colleagues[38] also demonstrated that subclinical rejection episodes were much lower in patients treated with tacrolimus, MMF, and steroids (2.6%) compared to historic controls treated with cyclosporine (30%).

Some tantalizing evidence exists that TAC is a potent and useful immunosuppressive agent for the prevention of acute rejection and reversal of steroid-resistant rejection. Recently, in a 5-year follow-up study, Vincenti and colleagues[39] demonstrated that tacrolimus-based therapy resulted in significantly reduced risk of graft failure, without an increase in the incidence of adverse events associated with long-term immunosuppression.

In another interesting study, Tan and colleagues[40] published their 3-year follow-up of the first 200 consecutive living donor kidney transplantation experiences under alemtuzumab pretreatment with tacrolimus monotherapy and subsequent spaced weaning. Unfortunately, 50 (25%) recipients had a total of 89 episodes of acute cellular rejection, making this approach experimental at this time.

Prospective, randomized studies are underway, examining the incidence of chronic allograft nephropathy, long-term renal function, steroid withdrawal, and cardiovascular risk factors comparing CsA and TAC.

Azathioprine

Azathioprine (AZA) is a purine analogue with a complex mechanism of action. It is metabolized in the liver to 6-mercaptopurine and 6-thioinosinic acid. Azathioprine can inhibit both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis by preventing interconversion among the precursors of purine synthesis and by inhibiting the initial steps of the *de novo* purine synthesis pathway through suppression of the enzyme glutamine phosphoribosyl pyrophosphate aminotransferase. It was widely used with steroids for maintenance immunosuppression before the introduction of cyclosporine to clinical transplantation.

The usual maintenance dose of azathioprine is 1 to 3 mg/kg/day as a single oral dose. One can adjust the dosage by monitoring the hematological side effects, not by assessing blood level measurements. The most important side effect of azathioprine is bone marrow suppression, which can usually be reversed by decreasing the dose or temporarily discontinuing the drug. Hepatitis, pancreatitis, and hair loss have also been reported. There is an important drug interaction with allopurinol, which by inhibiting the enzyme xanthine oxidase, can increase the toxicity of azathioprine. Therefore, simultaneous administration of azathioprine and allopurinol should be followed closely, and the dose of allopurinol may need to be reduced to 25% to 50% of the usual dose.

In two separate metaanalyses of triple therapy (cyclosporine, prednisone, azathioprine) versus double therapy (cyclosporine, prednisone), no graft outcome advantage could be statistically discerned for azathioprine in cyclosporine-based maintenance regimens.[9,10] The advent of the immunosuppressive agent MMF, which has decreased marrow toxicity, has entered the clinical arena of transplantation and gained popularity as part of the triple-drug regimen (cyclosporine or tacrolimus, MMF, and steroids). In one way, MMF has reduced acute rejection episodes by half compared to triple-therapy regimens that include azathioprine; however, the molecule is much more expensive, although generic preparations of mycophenolate mofetil have become available recently.

In a small study, Remuzzi and colleagues reported comparable outcomes, including graft loss, 72-month patient mortality, rejections, and adverse events between patients on AZA (n = 124) versus MMF (n = 124) therapy in combination with microemulsion formulation of cyclosporine.[41] In a much larger patient population, 49,666 primary renal allograft recipients reported to the United States Renal Data System, Meier-Kriesche and colleagues evaluated the association of long-term continuous MMF versus azathioprine therapy and renal allograft function, as measured by the slope of reciprocal creatinine.[42] They demonstrated that for 24-month continued therapy of MMF versus AZA, MMF was associated with a further decreased risk for a decline in renal function. In addition, MMF had a protective effect against reaching the serum creatinine threshold of 1.6 mg/dl beyond 12 months posttransplantation.

Mycophenolic Acid Derivatives

MMF is a semisynthetic derivative of mycophenolic acid produced by the fungus *Penicillium*. It was approved by the FDA in 1995 for use in rejection prophylaxis in kidney transplantation and has already replaced azathioprine in many centers around the world. MPA is poorly absorbed after oral administration; the use of MMF, the prodrug, improves the drug's bioavailability. After oral administration, MMF is rapidly and completely converted to mycophenolic acid in the stomach, which functions as a noncompetitive inhibitor of the rate-limiting enzyme inosine monophosphate dehydrogenase in the *de novo* purine biosynthesis pathway (Figure 36-2).

Because lymphocytes are highly dependent on the *de novo* pathway of purine synthesis and cannot efficiently use the salvage pathway, MMF, in theory, selectively inhibits the proliferation of T and B lymphocytes. A second action to inhibit intracellular glycosylation of peptides may prove equally important because many growth factors and their receptors require the addition of glycosyl residues to traffic from the endoplasmic reticulum to the cell surface.

The efficacy and safety of MMF in renal transplantation have been evaluated in three large multicenter studies.[43–45] These studies indicated that MMF reduces the incidence of acute rejection significantly compared to azathioprine or placebo when combined with cyclosporine and steroids. Side effects were greater in patients who received 3 g/day of MMF in all studies and included diarrhea, esophagitis, gastritis, leukopenia, and anemia. Nephrotoxicity, neurotoxicity, and hepatotoxicity have not been reported with MMF (Table 36-3).

Although MMF is a promising agent for both induction and maintenance therapy, it has also been used successfully as rescue therapy for biopsy-proven rejection refractory to treatment with high-dose steroids, OKT3, or both.[46] Its long-term graft survival advantage and effects on decreasing the risk of late acute rejection over azathioprine have also been shown in several recent studies.[42,47]

In addition, experimental animal data suggest that MMF may directly inhibit many mechanisms thought to be involved in chronic rejection. Although many authorities believe that MMF is an important adjunct to steroids and to some IL-2-blocking agents for early-maintenance therapy, the duration of treatment with this relatively expensive agent is unclear. Interestingly, ongoing trials are looking at steroid withdrawal and CNI minimization in patients taking MMF and at the use of MMF in combination with rapamycin and steroids in patients receiving expanded criteria donor kidneys.

Enteric-coated mycophenolate sodium (EC-MPS) is a slightly different MPA formulation that contains the active ingredient MPA as a sodium salt. It has been introduced to help alleviating MMF-related gastrointestinal (GI) side effects. It was approved by the FDA in 2004 in combination with cyclosporine and corticosteroids to prevent kidney

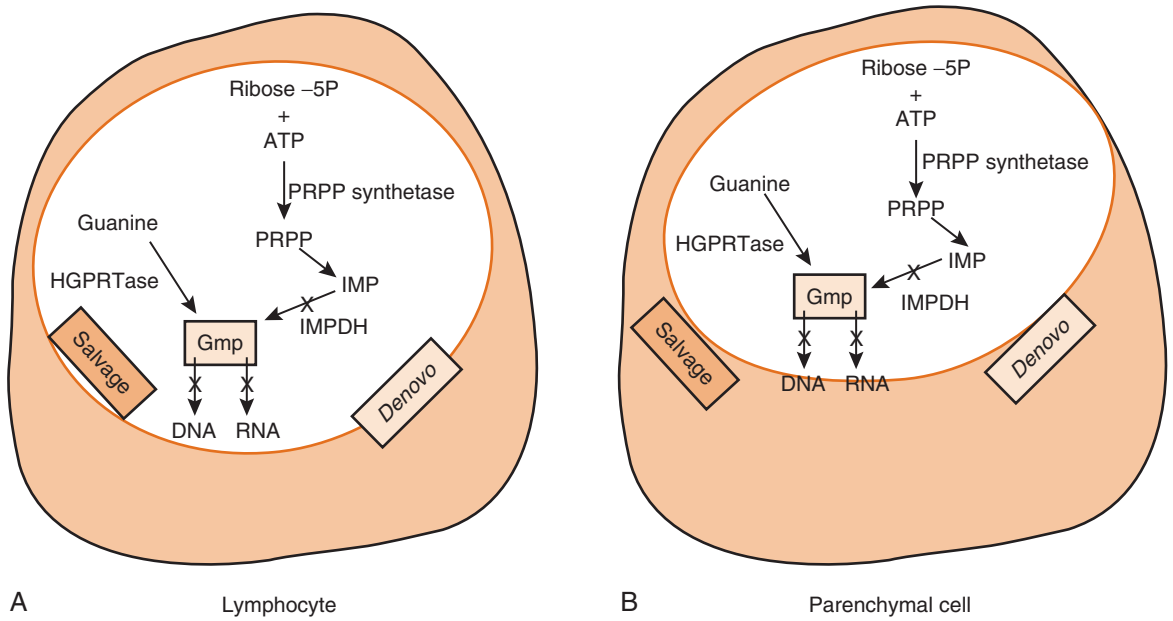


FIGURE 36-2 The mechanism of action of mycophenolate mofetil. **A,** Purine metabolism in the lymphocyte. **B,** Purine metabolism in the parenchymal cells. *ATP*, adenosine triphosphate; *DNA*, deoxyribonucleic acid; *Gmp*, Guanosine monophosphate; *HGPRTase*, hypoxanthine guanine phosphoribosyl transferase; *IMP*, inosine monophosphate; *IMPDH*, inosine monophosphate dehydrogenase; *PRPP*, 5-phosphoribosyl-1-phosphate; *RNA*, ribonucleic acid.

TABLE 36-3 Potential Adverse Effects of Mycophenolate Mofetil

Nausea
Anorexia
Diarrhea
Gastritis
Leukopenia
Anemia

transplant rejection. Delivery of MPA is delayed as expected from the enteric-coated form. It is available for oral use as either 180-mg or 360-mg tablets. EC-MPS does not release MPA under acidic conditions as in the stomach but is highly soluble in neutral pH conditions as in the intestine.

In a single-center, open-label, randomized, three-way crossover study of 24 stable white renal transplant patients receiving cyclosporine-based immunosuppression, Arns and colleagues[48] demonstrated that the EC-MPS 720-mg dose most closely approximated the MPA exposure of 1000 mg MMF. ES-MPS has been shown to provide equivalent efficacy to MMF when used in combination with cyclosporine microemulsion both in *de novo* kidney transplant patients and in stable kidney transplant patients who were converted to EC-MPS.[49–50] In an open-label, multicenter trial, Cibrik and colleagues followed 141 patients for 12 months using two different CsA concentration at 2-hour postdose (C2) in combination with EC-MPS, steroids, and basiliximab induction.[51] EC-MPS with low CsA C2 levels, corticosteroids, and basiliximab provided excellent renal function with good efficacy, though with a short follow-up. In another 6-month, open-label study, 63 stable kidney transplant recipients receiving tacrolimus were converted from MMF to EC-MPS.[52] Conversion from MMF to EC-MPS in these patients was found to be safe and well tolerated as well.

GI-adverse events after transplantation contribute significantly to MMF dose reductions that might lead to increased risk of graft failure. None of the early trials of EC-MPS were powered to show meaningful statistical differences in GI side effects compared to MMF. Although a study in 278 patients with a history of GI intolerance who were converted from MMF to EC-MPS demonstrated a reduction in GI-related symptom burden after the conversion, this was an open-label, short study.[53] A double-blind, placebo-controlled trial investigating the incidence and severity of GI events in kidney transplant patients has been completed but awaiting final publication.

The FDA has recently issued warnings regarding the use of MPA derivatives during pregnancy, which is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. Women of childbearing potential taking either MMF or EC-MPS must use contraception. Both of these drugs must be stopped 6 weeks prior to conception.

Sirolimus

Sirolimus (rapamycin) is a macrolide antibiotic produced by *Streptomyces hygroscopicus* that has demonstrated potent immunosuppressive activity in a number of studies in both animals and humans. It has been approved in 1999 by the FDA for prophylaxis of acute rejection in renal transplant recipients after a series of clinical trials from Europe and the United States demonstrated that when used in combination with cyclosporine and steroids, it decreased the incidence of acute rejection episodes in the early posttransplant period, compared to either azathioprine or placebo.

Another indication to withdraw cyclosporine when used in combination with sirolimus and steroids has also recently been approved by the FDA. Although it is structurally related to FK-506 and binds to FKBP, sirolimus has a distinct mechanism of action.[54] It forms a complex with the FKBP that binds with high affinity to the mammalian target of rapamycin (mTOR). This interaction causes dephosphorylation and inactivation of p70S6 kinase, which, when activated, stimulates the protein synthesis and cell cycle progression. This activity effectively blocks cytokine-driven (IL-2, IL-4, IL-15) T-cell proliferation by inhibiting G1 to S phase of the cell cycle. A clear synergistic effect with cyclosporine has been shown.

Although antagonistic to FK-506 in vitro, the intracellular pool of FKBP is so large that the two agents have been effectively used in renal transplant recipients in vivo. It has been demonstrated that simultaneous dosing of tacrolimus and sirolimus after transplantation is safe and that trough level monitoring is adequate to control therapy.

Sirolimus is a potent immunosuppressive drug with a relatively long half-life. It is metabolized by the same P450 enzyme system involved in the metabolism of CIs. It can be used both with and without a CI. Recent trials using sirolimus in combination with MMF and steroids demonstrated that sirolimus may be safely and effectively used as primary therapy for the prevention of acute rejection in kidney transplantation.[55] In another study, Oberbauer and colleagues[56] showed that early cyclosporine withdrawal followed by a sirolimus-steroids maintenance regimen resulted in long-term improvement in both renal function and blood pressure with no increased risk of graft loss or late acute rejection.

Reported side effects include headache, leukopenia, thrombocytopenia, hyperlipidemia, diarrhea, diabetes, delayed wound healing, and lymphocele (Table 36-4). There have been several reports of significant proteinuria due to sirolimus use in kidney transplant recipients not only in patients with established chronic allograft nephropathy but also in *de novo* live donor kidney transplant recipients at 6 months posttransplant.[57] Although the causes of rapamycin-induced proteinuria are not very clear, Vollenbroker and colleagues[58] demonstrated that prolonged use of rapamycin could affect the podocytes by decreasing the expression of the slit-diaphragm proteins nephrin and the cytoskeletal adaptor proteins leading to an imbalanced mTOR function. Rapamycin-induced proteinuria is not only observed in kidney transplant patients, but it was reported also in long-term cardiac transplant patients.[59] There have been reports of focal segmental glomerulosclerosis on kidney biopsies in patients on sirolimus as well. It has also been shown that it can exacerbate CNI-related nephrotoxicity when used in combination.

TABLE 36-4 Potential Adverse Effects of Rapamycin

Hypercholesterolemia
Leukopenia
Thrombocytopenia
Anemia
Arthralgias
Diarrhea
Wound complications
Lymphocele
Hypokalemia
Hypophosphatemia
Eyelid edema
Interstitial pneumonitis
Worsening of (DGF)
Proteinuria
Diabetes
Podocyte damage and FSGS

DGF, delayed graft function.

Interestingly, some animal studies showed that rapamycin inhibits smooth muscle cell proliferation and migration and chronic graft vessel disease in rat transplant models of chronic rejection, which raises questions that this agent might have a role in the prevention of clinical chronic rejection if started early after transplantation.[60] In a recent study, Morice and colleagues[61] showed that a rapamycin-eluting coronary stent compared to a standard stent showed considerable promise for the prevention of neointimal proliferation, restenosis, and associated cardiac events in patients with coronary artery disease.

There is evidence from animal studies that sirolimus can block regional tumor growth and metastatic progression of the tumor by showing an antiangiogenic effect linked to a decrease in production of vascular endothelial growth factor (VEGF) and to markedly inhibited response of vascular endothelial cells to stimulation by VEGF and increasing the expression of E-cadherin.[61–62] In another animal model, sirolimus inhibited the growth of EBV-associated B-cell lymphomas.[64] A multivariate analysis of posttransplant malignancies in 33,249 deceased donor primary solitary renal recipients reported by 264 kidney transplant programs to the Organ Procurement and Transplantation Network database from 1996 to 2001 was reported by Kaufmann and colleagues.[65] Maintenance immunosuppression with the mTOR inhibitor drugs was found to be associated with a significantly reduced risk of developing any posttransplant de novo malignancy (skin and solid) and nonskin solid malignancy. Thus, the use of sirolimus may be of value for the management of posttransplant malignancy. Future trials and the long-term results of current trials with sirolimus can shed light to this issue.

Recently, the efficacy and safety of sirolimus plus tacrolimus versus sirolimus plus cyclosporine were compared in 448 high-risk renal allograft recipients, such as blacks, repeat transplant recipients and patients with high-titer of panel-reactive antibodies. At 12 months, biopsy-confirmed acute rejection rate (13.8% vs. 17.4%) and graft survival rate (89.7% vs. 90.2%) were similar (SRL+TAC vs. SRL+CsA, respectively).[66] Interestingly, in on-therapy patients, the glomerular filtration rate was significantly higher in SRL+TAC at most time points.

Sirolimus has also been used in patients with delayed graft function. By using a CI-free protocol of antibody induction, sirolimus, MMF, and prednisone in recipients with marginal donor kidneys or delayed graft function, Shaffer and colleagues[67] demonstrated low rates of acute rejection and excellent early patient and graft survival. Conversely, there are concerns that when used with a CNI, sirolimus could exacerbate delayed graft function; this requires further study. Sirolimus use has also been reported in hemolytic-uremic syndrome, in steroid-free regimens, as a rescue agent in

severe acute rejection, and as a substitute for CNI in patients with chronic rejection.

Everolimus or SDZ RAD is a derivative of sirolimus. Its half-life is shorter than that of sirolimus with similar side effect profile. Clinical experience with everolimus and low-dose CNI in heart and kidney transplant recipients suggests that this is a potent and effective immunosuppressive drug. But similar to sirolimus, in the rat remnant kidney model, Vogelbacher and colleagues[68] demonstrated that everolimus treatment could worsen chronic disease progression as assessed by increased proteinuria, glomerulosclerosis, interstitial fibrosis, glomerular inflammation and decreased creatinine-clearance. They concluded that the result was due to a markedly increased fraction of glomeruli with a defective glomerular architecture in the everolimus group, adding more information to the current discussion on mTOR inhibitors and proteinuria. Although it does not have FDA approval in the United States yet, it is approved for use in Europe and Asia, and trials are in progress in which it is being tested not only in transplantation but also in patients with different types of cancer such as renal cell carcinoma, breast cancer, and colon cancer.

Biological Agents

Recently, much research has been conducted to develop antibodies and fusion-receptor proteins with long half-lives and prolonged biological effects for maintenance therapy to replace oral agents, especially CNIs, that are associated with significant toxicities. We will review the most studied and promising agents briefly.

Belatacept (LEA29Y)

Belatacept is a selective costimulatory blocker that binds to CD80/CD86 surface ligands of antigen-presenting cells, selectively blocking the activation of T-cells. The interaction of CD80 and CD86 with the surface costimulatory receptor CD28 of T-cells is required for full activation of T-cells. It is a fusion protein that is derived from abatacept and composed of the extracellular portion of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the constant-region fragment of human IgG1 immunoglobulin (CTLA4Ig). It differs from abatacept by only two amino acids and has greater binding avidity to CD80 and CD86. Belatacept provides more potent inhibition of T-cell activation than abatacept.

In a partially blinded, randomized, multicenter phase 2 study in 218 patients, Vincenti and colleagues[69] demonstrated that the incidence of acute rejection was similar among three groups of patients: 7% for intensive belatacept, 6% for less-intensive belatacept, and 8% for cyclosporine. At 12 months, both renal function and histology was much better in patients treated with belatacept, raising the possibility of eliminating CNIs without compromising transplant outcomes. An important issue is that belatacept has to be given intravenously, which might be helpful in patient compliance with immunosuppressive regimens. Two phase III trials with belatacept are currently ongoing: one for patients receiving kidneys from extended criteria donors (ECD) and one for patients receiving kidneys from living donors and standard criteria kidneys from deceased donors. The results of these two phase II trials, and other studies such as conversion study from CNIs to belatacept, pairing belatacept and sirolimus, and using alemtuzumab along with belatacept in kidney transplant recipients, are eagerly awaited.

Two other biological are being developed for use in transplantation: One is efalizumab, a humanized antilymphocyte-associated function-1 (LFA1) antibody that binds to the CD11a chain of LFA-1and and blocks the interaction between LFA-1 and intercellular adhesion molecule (ICAM),[70] and the other is alefacept, a recombinant LFA-3-IgG fusion protein that blocks the interaction between LFA-3 and CD2. In a phase I/II study of 38 kidney transplant recipients administered subcutanously, efaluzimab was found to be quite effective with low acute rejection rates, but unfortunately three patients (8%) developed posttransplant lymphoproliferative disease, and all were treated with the higher-dose efalizumab and full-dose cyclosporine.[71] Both drugs are approved by the FDA for use in psoriasis. Large, multicenter, phase II trials are underway.

Studies using small nonprotein molecules such as ISA247, a structural analogue of cyclosporine; CP690,550, which is a janus kinase-3 (JAK3) inhibitor; and AEB071, which is a protein kinase C (PKC) inhibitor, are also in progress testing the effects of these drugs on different intracellular signaling pathways, which play a significant role in immune responses. There are also other molecules being tested in preclinical studies targeting B-cell, reperfusion injury, complement inhibition, and different cytokine pathways.

Leflunomide

Leflunomide is a synthetic isoxazole derivative with antiinflammatory and antiviral properties that inhibits pyrimidine nucleotide synthesis with secondary effects on IL-2, transforming growth factor alpha, and antibody production. It has been reported to prevent acute rejection and delay progression of chronic allograft nephropathy and prolong graft survival in different animal models. In addition, it has inhibitory effects on herpes virus replication. Interestingly, despite the lack of controlled and randomized trials, case reports and small observational studies suggest that in addition to reduction of immunosuppression, leflunomide might be useful in reducing the BK viremia/viruria and graft loss in patients with BK nephropathy.[72] Side effects include anemia, gastrointestinal toxicity, elevated liver enzymes, and weight loss. Preclinical studies in kidney transplant recipients testing an analogue of leflunomide, FK778, unfortunately had disappointing results.

SUMMARY

For many years, the mainstay of immunosuppressive therapy in kidney transplantation has been the combination of Sandimmune, azathioprine, and prednisone. The introduction of cyclosporine microemulsion, tacrolimus, MMF, sirolimus, and leflunomide for maintenance therapy has provided transplant physicians with a wide variety of choices in order to be able to pick and choose the best individual immunosuppressive regimen for the individual patient.

Currently, numerous potent immunosuppressive agents targeting different steps of T-cell activation are being tested. Questions that remain unanswered are whether these new agents are providing more specific immunosuppression, what is the best combination to achieve maximum efficacy and minimum harm, whether these agents can prevent chronic allograft nephropathy and improve long-term graft survival, and whether these agents affect tolerance induction.

ACKNOWLEDGMENT

A special note of appreciation is due to Mrs. Nadine Cline, whose patience in dealing with cross-country manuscript preparation was most important for completion of this project. We remember her fondly.

A full list of references are available at www.expertconsult.com.

Chapter 37

DIAGNOSIS AND THERAPY OF GRAFT DYSFUNCTION

Phuong-Thu T. Pham, M.D., Cynthia C. Nast, M.D., Phuong-Chi T. Pham, M.D. and Gabriel Danovitch, M.D.

Kidney transplantation is the treatment of choice for virtually all suitable candidates with end-stage renal disease due to its improved survival and quality of life compared to dialysis. Ideally, a renal allograft recipient receives a high-quality donor kidney, undergoes a smooth surgical grafting, develops an immediate posttransplant diuresis with a steady improvement of renal function, and achieves excellent graft function and survival. Although such an ideal course is realized for many patients, graft dysfunction is an incessant threat throughout the graft lifetime for many others. The etiology and management of graft dysfunction vary over time. Hence, the differential diagnosis is best approached by considering the different posttransplant periods. In this chapter, graft dysfunction will be discussed in three arbitrarily defined phases:

1. *Delayed graft function* (DGF), occurring in the immediate posttransplant period
2. *Early graft dysfunction*, occurring in the first 2 to 3 posttransplant months

3. *Late graft dysfunction*, occurring thereafter

DELAYED GRAFT FUNCTION

Definition

The term *delayed graft function* (DGF) has been used to describe marginally functioning grafts that recover function after several days to weeks. Delayed graft function should be distinguished from *primary nonfunction*, where the kidney allografts never function and allograft nephrectomy is usually indicated. Despite the exponential growth in renal transplantation, no universally defined criteria for DGF have been established. Nevertheless, various indices, including urine volume, dialysis requirement, and serum creatinine, have been used to define "delayed graft function."

In general, a urine output greater than 20 ml/kg/day in the immediate postoperative period is a good clinical indicator of adequate renal function. Using urine output as an indication for early allograft function, however, is limited in cases where large urine volume is still being produced by the native kidneys. A large urine output from the native kidneys in the immediate postoperative period may be mistaken for an early functioning graft. Alternatively, no increase in urine output postoperatively does not necessarily indicate DGF.

The most frequently used definition of DGF is the requirement for dialysis in the first posttransplant week. In studies evaluating the causes and management of DGF, a modified definition of "the need for more than one dialysis" is sometimes applied to take into account the need for a single postoperative dialysis for the management of hyperkalemia, or volume overload, or the safe administration of blood products.[1] Using the need for dialysis alone to define DGF, however, may lead to underdiagnosis, particularly if there is some residual native kidney function. An elevated serum creatinine concentration of greater than 400 mol/L (>4.5 mg/dl) one week after transplantation has been suggested to be a more sensitive and specific measure of DGF.[2]

More recently, it has been proposed that creatinine reduction ratio on postoperative day 2 (CRR2) should be used to define nondialyzed DGF. CRR2 has been demonstrated to correlate significantly with renal function during the first year. Similar to DGF requiring dialysis (D-DGF), nondialyzed DGF (CRR2-defined DGF) had a negative impact on renal function and graft survival independent of acute rejection episodes.[3] The term *slow graft function* (SGF) is sometimes used to describe nonoliguric patients who usually do not require dialysis but who experience a delayed fall in serum creatinine. Various suggested definitions of DGF-SGF[1–5] are shown in Table 37-1.

TABLE 37-1 Definitions of Delayed Graft Function–Slow Graft Function (DGF-SGF)

- Need for dialysis in the first posttransplant week*
- Need for >1 dialysis in the first week* (to account for the need for a single dialysis for ↑ K^+ or volume overload)
- SCr > 400 µmol/L (4.5 mg/dL) 1 week after transplantation
- SCr > 3 mg/dl on posttransplant day 5
- Creatinine reduction ratio on postoperative day 2 (CRR2)
- Absence of spontaneous ↓ SCr at day 1
- <10%-30% ↓ in SCr in the first 24-72 hours
- Time needed to reach a GFR of >10 ml/min
- Time for SCr to ↓ by 50% ($t_{1/2}$ SCr)
- Urine output <1000 ml the 1st 24 hours

*Most frequently used definition(s)
GFR, glomerular filtration rate; *SCr*, serum creatinine.

Differential Diagnosis

Although most deceased donor kidneys with DGF are afflicted with the clinicopathological entity of acute tubular necrosis (ATN), it should be noted that these terms are not synonymous, and other causes of DGF should be excluded.

TABLE 37-2 Differential Diagnosis of Delayed Graft Function

1. **Prerenal (or preglomerular type)**
   - Volume contraction
   - Nephrotoxic drugs (see text)
2. **Vascular complications**
   - Arterial or venous thrombosis
   - Renal artery stenosis
3. **Intrinsic renal**
   - Acute tubular necrosis
   - Accelerated acute or acute rejection
   - Thrombotic microangiopathy
   - Recurrence of primary glomerular disease (particularly FSGS)
4. **Postrenal**
   - Catheter obstruction
   - Perinephric fluid collection (lymphocele, urine leak, hematoma)
   - Ureteral obstruction
     - Intrinsic (blood clots, poor reimplantation, ureteral slough)
     - Extrinsic (ureteral kinking)
   - Neurogenic bladder
   - Benign prostatic hypertrophy

The differential diagnosis of DGF is shown in Table 37-2. Similar to the nontransplant setting, a systematic approach to the evaluation of DGF may be divided into prerenal (or preglomerular type), intrinsic, and postrenal causes. Posttransplant ATN is essentially a diagnosis of exclusion. Although uncommon, vascular causes of DGF must be excluded, particularly in the early postoperative period (see Table 37-2).

Prerenal Causes of Delayed Graft Function

Severe intravascular volume depletion or a significant fall in blood pressure is usually suggested by a careful review of patients' preoperative history and intraoperative report. Knowing patients' dialysis dry weight and preoperative weight may be invaluable in the assessment of their volume status in the immediate postoperative period. Intraoperative Swan-Ganz placement for continuous monitoring of central venous or pulmonary wedge pressure may be useful in assessing the volume status of patients with cardiomyopathy and/or coronary artery disease.

Both calcineurin inhibitors (CNI) cyclosporine and, to a lesser extent, tacrolimus have been shown to cause a dose-

related reversible afferent arteriolar vasoconstriction and "preglomerular type" allograft dysfunction that manifests clinically as delayed recovery of allograft function. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, Amphoterecin B, nonsteroidal antiinflammatory drugs (NSAIDS), and radiocontrast dye are commonly used drugs that may potentially precipitate or exacerbate acute preglomerular type allograft dysfunction. A thorough chart review should focus on the recent use of nephrotoxic medications and perioperative blood pressure curves.

Intrinsic Renal Causes of Delayed Graft Function

Intrinsic renal causes of DGF typically include ATN, acute rejection, infection, thrombotic microangiopathy, or recurrence of glomerular diseases affecting the native kidneys.

Acute Tubular Necrosis

Posttransplant acute tubular necrosis is the most common cause of DGF. The two terms are often used interchangeably, although not all cases of DGF are caused by ATN. The incidence of ATN varies widely among centers and has been reported to occur in 20% to 25% of patients (range 2% to 60%).[4–11] The difference in the incidence reported may, in part, be due to the more liberal use of organs from marginal donors by some centers but not by others, the difference in the criteria used to define DGF, or both. Unless an allograft biopsy is performed, posttransplant ATN should be a diagnosis of exclusion. Both donor and/or recipient factors are important determinant(s) of early allograft dysfunction (Table 37-3). Pretransplant peritoneal dialysis treatment modality has been suggested to reduce the incidence and severity of delayed recovery of renal function after transplantation independent of cold ischemia time and volume status.[12]

TABLE 37-3 Risk Factors for Delayed Graft Function (DGF) Due to Acute Tubular Necrosis (ATN) in Deceased Donor Renal Transplantation

DONOR FACTORS	RECIPIENT FACTORS
PREMORBID FACTORS	***PREMORBID FACTORS***
Age (<10 or >50)	Age
Donor hypertension	African Americans (compared to whites)
Donor macrovascular or microvascular disease	Peripheral vascular disease
Cause of death (cerebrovascular vs. traumatic)	Hemodialysis (compared to peritoneal dialysis)
	Duration of dialysis before transplant
	Presensitization (PRA >50)
	Reallograft transplant
	Body mass index >30 kg/m^2
	Hypercoagulability state*
PREOPERATIVE DONOR CHARACTERISTICS	***PERIOPERATIVE AND POSTOPERATIVE FACTORS***
Brain-death stress	Hypotension, shock
Prolonged used of vasopressors	Recipient volume contraction
Preprocurement ATN	Early high dose calcineurin inhibitors
Donation after cardiac death (DCD)	Sirolimus**
Nephrotoxic agents	+/– early OKT3 use
ORGAN PROCUREMENT SURGERY	
Hypotension prior to cross-clamping of aorta	
Traction on renal vasculatures	
Cold storage flushing solutions	
KIDNEY PRESERVATION	
Prolonged warm ischemia time (+/– contraindication to transplantation)	
Prolonged cold ischemia time	
Cold storage vs. machine perfusion	
INTRAOPERATIVE FACTORS	
Intraoperative hemodynamic instability	
Prolonged rewarm time (anastomotic time)	
Leiden mutation or antiphospholipid antibodies	

*Such as presence of factor V
**May prolong the duration of DGF

Pathogenic Mechanisms

ATN found in the posttransplant setting is essentially an ischemic injury that may be synergistically exaggerated by both immunological and nephrotoxic insults. All transplanted kidneys are subjected to injury at various steps in the transplantation process—from donor death to organ procurement, surgical reanastomosis, and postoperative course. Understanding, identifying, and addressing the potential for injuries at every step of this complex process are critical to the prevention of posttransplant ATN. Some degree of ischemic injury is invariably unavoidable in deceased donor renal transplantation.

Much can be inferred about the cellular and molecular mechanisms of posttransplant ATN from observations in nontransplant animal models and human native kidneys.[13–16] In essence, during ischemia, cellular metabolism continues, and the resulting shift to anerobic metabolism leads to accumulation of lactic acid, failure of Na^+-K^+ATPase pumps, loss of cell polarization, cell swelling, and subsequent lysis with release of cytotoxic oxygen-free radicals. In organ transplantation, suppression of metabolism is essential to prolong the time of ischemia that a retrieved organ can sustain. Reducing the core temperature of the kidney to less than 4°C results in reduction in enzymatic activities and metabolism to 5% to 8% in most cells.[17] Early experiences demonstrated that simple ice-cooling of kidneys preserved renal function for 12 hours.[18] With the use of a preservation solution, cold ischemia time can be significantly prolonged and the rate of DGF and *primary nonfunction* reduced (discussed under Organ Preservation).

Because of the unique sequence of events leading to organ transplantation, the transplanted kidney is particularly susceptible to reperfusion injury. The reintroduction of oxygen into tissues with high concentration of oxygen free radicals leads to the production of superoxide anion and hydrogen peroxide and subsequent lipid peroxidation of cell membranes. This process may be responsible for the commonly observed clinical sequence where an early posttransplantation diuresis is followed by oliguria within hours.

Damage to the vascular epithelium leads to the release of vasoactive molecules that may be responsible for the hemodynamic changes typical of ATN.[15] The term *vasomotor nephropathy* may be more appropriate than ATN because it describes a physiologically altered state that may not be necessarily accompanied by tubular necrosis histologically.[16] As a result of increased renovascular resistance and decreased glomerular permeability, the glomerular filtration rate (GFR) falls. In ATN, both tubular obstruction from cellular debris and intrarenal edema-induced increase in intrarenal pressure and subsequent blood flow reduction diminish the GFR.[19] Although blood flow to the renal cortex is reduced, there is relatively greater reduction in GFR and tubular function, which accounts for the typical findings of "good perfusion and poor excretion" on scintigraphic studies.[20] The alterations in vascular resistance and increased intracapsular pressure result in the increased resistive index and reduced or reversed diastolic blood flow observed on Doppler ultrasound.

Although ischemic injury has been regarded as a major risk factor for the development of posttransplant ATN, several lines of evidence suggest that immunological factors may be equally important. The former is suggested by the observation that the incidence of DGF was significantly higher among recipients of deceased donor kidneys compared to living-donor transplants and the latter by the observation that DGF is more prevalent in recipients of reallograft transplants compared to those of primary transplants, particularly in cases with high levels of preformed panel-reactive antibodies.[4,21] A positive flow cytometry crossmatch in the absence of a positive standard complement-dependent cytotoxicity crossmatch has also been shown to be associated with a greater incidence of ATN and delayed improvement of the posttransplant plasma serum creatinine level.[22] Presumably, the immunological factors render the newly transplanted kidney more susceptible to ischemic injury.

THE EFFECT OF ACUTE TUBULAR NECROSIS ON HOST IMMUNOGENECITY

Some but not all evidence suggests that ATN may contribute to the upregulation of inflammatory cytokines and increased expression of class I and II major histocompatibility (MHC) antigens, thus increasing the immunogenecity of the transplanted kidney and its susceptibility to both acute and chronic rejections.[23,24] Nitric oxide produced by the inducible nitric oxide synthase (iNOS) enzymes in response to ischemic cell injury has been suggested to play a role in the link between ischemic reperfusion injury and graft rejection.[26] Renal epithelial regeneration mediated by growth factors and cytokines, such as epidermal growth factors (EGF) and transforming growth factor β (TGF-β), following ischemic damage may facilitate the development of the low-grade inflammation and fibrosis observed with chronic rejection.[27] Injury in the form of ATN leads to inflammation, which, in turn, facilitates an immune response and adds further insults to the initial injury.[21,23]

The stress of brain death itself likely has a similar effect to ATN associated risks for allograft rejections. In a rat study, explosive brain death has been shown to be associated with upregulation of macrophage (interleukin 1 [IL-1], [IL-6], and tumor necrosis factor α) and T-cell-associated products (IL-2 and IF-α) in peripheral organs, rendering them more susceptible to subsequent host inflammatory and immunological responses.[25]

Immunohistochemical analysis of pretransplant donor biopsies from deceased and living organ donors (controls) demonstrated increase E-selectin expression and interstitial leukocyte accumulation in deceased donor kidneys versus controls, suggesting that brain death initiates an inflammatory reaction in the human kidney.[28] It is conceivable that early injury may render brain-dead donor kidneys more vulnerable to adverse physiological and immunological events following transplantation. Highly matched kidneys have been suggested to be less susceptible to the harmful effects of DGF, presumably because ATN exposes the mismatched kidney to a more aggressive immune attack.[29]

A number of studies have shown that in the long-term ATN kidneys that do not develop rejection do as well as non-ATN kidneys that do not develop rejection, lending support to the theory that it is the immunological consequences of ATN that are responsible for its prognostic significance.[30] Yet, studies on the impact of DGF (presumably due to ATN) with or without early acute rejection on long-term allograft survival have yielded variable and conflicting results (discussed in a later section).

Histology

ATN in the allograft is similar to that in the native kidney. Tubular epithelial cells show necrosis, often with sloughed, degenerated, or apoptotic epithelial cells in the tubular lumina, a feature more prominent in ATN involving transplanted kidneys.[31] Proximal cell brush border staining of proximal tubular epithelium is focally absent with flattening of tubular cells, and there may be regeneration in the form of mitotic figures (Figure 37-1).[32] Calcium oxalate deposition may accumulate in tubular lumina and is associated with early graft dysfunction and prolonged tubular cell necrosis.[33] The interstitium is variably edematous, with a minimal or

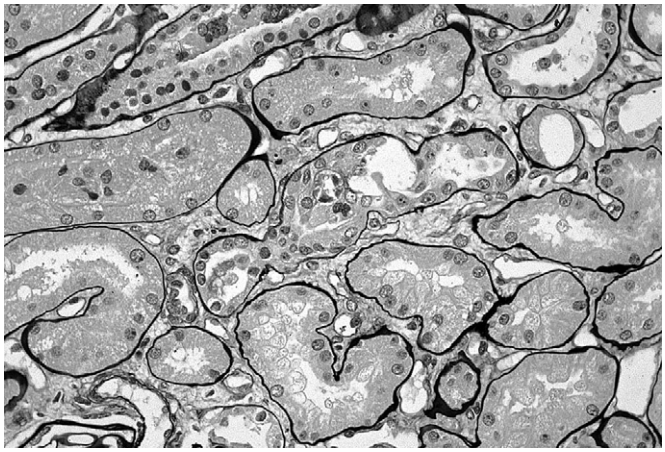


FIGURE 37-1 Acute tubular necrosis. Tubular cells show flattening and necrosis and focally are desquamated into the tubular lumina. The central tubule contains calcium oxalate in the lumen, a product of cellular debris (Jones methenamine silver × 250).

patchy interstitial lymphocytic infiltrate; however, there is no associated inflammation in the walls of tubules. No specific changes of glomeruli or the vasculature are found in ATN.

Prediction and Prevention

Kidneys from living biologically related or unrelated donors rarely suffer from DGF, whereas DGF in recipients of deceased donor varies from 2% to 60%.[4,6–11] Living donors are extensively evaluated to ensure optimization of their health, their kidneys, and the circumstances of organ harvesting to permit minimalization of ischemic damage to the organ. On the contrary, the uncontrolled circumstances surrounding sudden death and the complexities of the deceased donor organ procurement process inevitably result in varying degrees of ischemic damages that adversely affect renal function.

Donor factors before the procurement of deceased donor organs are important predictors of early and late graft function. Kidneys from older donors have a higher incidence of ATN,[34] a finding that is reminiscent of the clinical observation that older patients in the nontransplant setting are also more susceptible to ATN when faced with ischemic or nephrotoxic insult.[35] The common factor linking older age to ATN is probably diminished capacity of the aging vasculature to vasodilate adequately to protect the kidney from anoxic damage.

In this respect, donor death from traumatic injury is less likely to be associated with ATN than death from cerebrovascular causes because the trauma victim is more likely to have been younger and healthier than a stroke victim.[36] Nonetheless, even the "ideal" trauma victim is likely to have experienced an episode of hypotension and, not uncommonly, suffered a fluctuating or deteriorating renal function. While kidneys from young donors typically recover from pretransplantation injury, the prognosis for kidneys from older donors with pretransplantation impairment of renal function is often poor, and such kidneys were previously rejected by many centers. However, the critical shortage of donor organs has resulted in increased use of kidneys from expanded criteria donors (ECD). These kidneys are defined by donor characteristics that are associated with a 70% greater risk of kidney graft failure when compared to a reference group of nonhypertensive donors of ages 10 through 39 years whose cause of death was not cerebrovascular accident (CVA) and whose terminal creatinine was less than or equal to 1.5 mg/dl. The donor factors associated with this increased relative rate of graft failure include age 60 or older, or ages 50 to 59, with at least two comorbid factors. The latter may include CVA as a cause of death, hypertension, and/or terminal creatinine greater than 1.5 mg/dl (Table 37-4).

To optimize allograft outcome using these "marginal" kidneys, the United Network of Organ Sharing (UNOS) has implemented a system to minimize cold ischemia time and to expedite ECD kidney placement. Currently, the allocation of ECD kidneys is based on prior identification of and consent by ECD waitlisted candidates, preprocurement tissue typing of ECD kidneys, and abbreviated time period (2 hours) for placement of zero mismatched ECD kidneys.

TABLE 37-4 Factors that Determine Expanded Criteria Donors (Adapted from UNOS)

DONOR CONDITION	DONOR AGE CATEGORIES	
	50-59	*≥60 or older*
CVA + HTN + Creat >1.5	X	X
CVA + HTN	X	X
CVA + Creat >1.5	X	X
HTN + Creat >1.5	X	X
CVA		X
HTN		X
Creatinine >1.5		X
None of the above		X

Creat over 1.5, creatinine over 1.5 mg/dl; *CVA*, CVA was cause of death; *HTN*, history of hypertension at any time; *X*, expanded criteria donor.

If no zero antigen mismatch transplant candidate is identified, the ECD kidney will be allocated to all other "preidentified" candidates by waiting time alone, first locally, then regionally, and then nationally.

Despite the efforts to decrease cold ischemia time, the use of ECD kidneys inevitably increases the incidence of posttransplantation ATN. Similarly, attempts to bolster the deceased donor pool by the use of donor after cardiac death (DCD) that are by definition susceptible to variable degrees of warm ischemic damage have resulted in an increased incidence of DGF. In a single center study consisting of 456 renal transplants performed during a 10-year period, DGF has been reported to occur in 17% of heart-beating deceased donor kidneys compared to 95% of DCD kidneys. Nonetheless, graft survival in the DCD recipients with DGF was significantly better at 3 years compared to recipients of a heart-beating donor (HBD) renal transplant that developed DGF[37] (84% vs. 73%, respectively; $p < 0.05$) and at 6 years (84% vs. 62%, respectively). Although the superior outcome of DCD kidneys compared to that of HBD appears paradoxical, it has been proposed that brainstem death causes cytokine release and inflammatory reactions, events that do not occur in donation after cardiac death.[37] Analysis of the U.S. Renal Data System revealed that recipients of DCD donor organs experienced nearly twice the incidence of DGF compared to heart-beating donors (42.3% vs. 23.3%, respectively). Nonetheless, DCD donor transplants experienced comparable allograft survival when compared with heart-beating deceased donor transplant at 6-year follow up (73.2% vs. 72.5%, respectively; P = NS). Interestingly, there was a trend for better patient survival at 6 years for DCD compared to HBD renal transplant recipients. Significant risk factors for allograft loss for DCD donor organ recipients include repeat transplant, DGF, donor age older than 35 years, and head trauma as a cause of initial injury.[38]

It should also be noted that not all DCD donor organs are equivalent. Donor after cardiac death can occur under a "controlled" or "uncontrolled" circumstance and is categorized into four groups based on Maastricht criteria (Table 37-5). Under a controlled circumstance (Category III and IV), donor warm ischemia time is relatively shorter and more predictable than that of uncontrolled DCD donor kidneys (Category I and II). In a study designed to determine the impact of ischemic

TABLE 37-5 Maastricht Criteria for DCD Donors

CATEGORY	CONTROLLED	UNCONTROLLED
I		Dead on arrival
II		Unsuccessful resuscitation
III	Withdrawal of life support	
IV	Cardiac arrest after brain stem death	

DCD, donor after cardiac death.

injury on renal function of kidneys procured from different categories of DCD kidneys, Gok and colleagues[39] demonstrated a higher incidence of DGF and ATN in the uncontrolled compared to that of the "controlled" DCD donor groups. The incidence of DGF and ATN for Maastricht categories II, III, and IV were 83.8%, 67.4%, and 0%, respectively (ANOVA $p < 0.05$), and 81.1%, 65.2%, and 50%, respectively (ANOVA p = NS). Nonetheless, renal function at 3 months and 1-year graft survival were comparable among all categories studied.

DCD kidneys with acute kidney injury (AKI) before cardiac arrest have been considered to be at particularly high risk for DGF and primary nonfunction and are often rejected and discarded. To maximize use the of such kidneys, machine perfusion parameters and viability testing have been used by a number of centers to assess the extent of kidney damage and to predict graft function. In a small retrospective study consisting of 49 renal transplant recipients from category III DCD, Sohrabi and colleagues[40] found no significant difference in DGF and rejection rates between those with "low-severity prearrest AKI" (defined by RIFLE classification; Table 37-6) and those without AKIRF. One donor was classified as RIFLE I (Injury) and the remainder as RIFLE R (Risk). Recipients' GFR at 12 months was 44 ± 17.1 and 45.2 ± 14.7 ml/min/1.73 m^2 from donors with (n = 9) and without AKIRF (n = 40), respectively. All kidneys but one had hypothermic machine perfusion and viability testing prior to transplantation. Of nine kidneys from donors with prearrested evidence of AKIRF, one resulted in primary nonfunction. In the latter case, the donor renal artery was damaged during recovery of organs, preventing machine perfusion and viability testing. Based on these results, the authors suggested that selected controlled DCD donor kidneys with low-severity prearrest AKIRF can be used provided that some form of viability assessment has been implemented. Suggested parameters indicating a viable kidney include a Perfusion Flow Index (PFI)—defined as the flow per 100 gram renal mass divided by the systolic pressure, of greater than 0.4 ml/min/100 g/mmHg and perfusate glutathione-S-transferase level (an enzymatic marker of ischemic injury) of less than 100 International Units/100 g of renal mass.

DUAL KIDNEY TRANSPLANTATION

In selected cases, dual transplant of ECD kidneys have been offered to older recipients with excellent short- and intermediate-term allograft outcomes. Early reports from a single-center study demonstrated comparable allograft function and incidence of graft loss at 4 years among dual ECD kidney recipients (n = 10) and age-matched single-deceased donor kidney recipients (n = 10).[41] Similarly, a recent analysis of the OPTN/UNOS database consisting of 625 dual kidney transplants (DKT) and 7686 single ECD transplants demonstrated comparable 3-year overall graft survival between DKT and single ECD transplant recipients (79.8% vs. 78.3%, respectively).[42] Compared to the ECD donor group, the DKT donor group was older (mean age 64.6 ± 7.7 years vs. 59.9 ± 6.2 years) and consisted of more African Americans (13.1% vs. 9.9%) and more diabetic donors (16.3% vs. 10.4%, $p < 0.001$). Mean cold ischemia time was longer in DKT (22.2 ± 9.7), but the rates of DGF were lower compared to ECD transplants (29.3% vs. 33.6%, P = 0.03).

It has been suggested that the salutary effect of dual kidney transplant is due to the greater viable nephron mass. Experimental studies in rats have shown that increasing the number of viable nephron mass by dual kidney transplantation prevented the progressive deterioration in renal function that occurred in control rats receiving a single kidney.[43] The concept of nephron dosing has also sparked interest in the use of dual marginal kidneys from DCD donors to minimize discarding potential donor organs. In a subset of DCD donor kidneys that do not satisfy the viability criteria for single organ transplantation, dual organ grafts have resulted in short-term allograft function that were comparable to that of their single organ counterpart. In a retrospective study consisting of 23 dual DCD donor renal transplants and 115 single DCD transplants, Navarro and colleagues[44] demonstrated similar GFR in the dual and single transplant groups at 3- and 12-month follow-ups (dual: 46.2 and 45.5 ml/min/1.72 m^2, respectively, and single: 40.7 and 43.0 ml/min/1.72 m^2, respectively). Studies with longer-term follow-ups are needed.

TABLE 37-6 RIFLE Classification of Acute Kidney Injury (AKI)

CLASSIFICATION	GFR CRITERIA	URINE OUTPUT CRITERIA	
Risk	↑ SCr × 1.5 or GFR ↓ > 25%	UO <0.5 ml/kg/h × 6 hrs	*High sensitivity*
Injury	↑ SCr × 2 or GFR ↓ > 50%	UO <0.5 ml/kg/h × 12 hrs	
Failure	↑ SCr × 3 or GFR ↓ > 75% or SCr > 4 mg/dl	UO <0.3 ml/kg/h × 24 hrs or anuria × 12 hrs	
Loss	Persistent AKI = complete loss of kidney function >4 weeks		*High specificity*
ESRD	End-Stage Renal Disease (>3 months)		

AKI, acute kidney injury; *GFR*, glomerular filtration rate; *SCr*, serum creatinine; *UO*, urine output; .

ORGAN PROCUREMENT AND PRESERVATION

Early ischemic injury adversely affects both short- and long-term allograft function and/or survival. In deceased donor kidneys, the earliest injury begins with organ procurement and preservation. The purpose of donor management is to maintain adequate organ perfusion before rapid cooling and flushing of the kidneys to minimize warm ischemia. The warm ischemia time refers to the period between circulatory arrest and the commencement of cold storage.[45] Ischemia at body temperature can be tolerated for only a few minutes, after which irreversible injury begins to occur and the organ becomes nonviable within 30 minutes. Cold ischemia time refers to the period of cold storage or machine perfusion. Fortunately, for the purpose of transplantation, anaerobic metabolism can maintain renal cellular energy requirements for up to 48 hours, provided the organ is cooled to about 4°C with an appropriate preservation solution.[46] Increasing both the warm and cold ischemic time leads to a progressive decline in graft survival rates and an increase in the incidence of DGF. Ideally, kidneys are transplanted without significant warm ischemia and with cold ischemia time less than 24 hours. In DCD donation, rapid institution of cooling to reduce warm ischemia is particularly vital because of the absence of blood circulation. Hypothermia-induced reduction in tissue metabolism (for every 10°C of organ cooling, metabolism is decreased by approximately 50%) alleviates ischemic injury.[17,47]

ORGAN PRESERVATION

The EuroCollins Solution versus the University of Wisconsin Solution

Although the method of kidney preservation differs among centers, simple cold storage is the most widely used technique. The goal of preservation is to maximize ischemic tolerance during anaerobic metabolism and to minimize ischemic reperfusion injury. The EuroCollins solution was used for many years for kidney flushing and preservation until the 1990s, when the University of Wisconsin solution began to gain popularity[10,45] for its superiority in reducing the rate of DGF and extending cold ischemia time. In a randomized clinical trial comparing the EuroCollins with the University of Wisconsin solution in deceased donor renal transplants, DGF was significantly lower (23% vs. 33%, $p = 0.003$) and 1-year graft survival significantly higher (88.2% vs 82.5%, $p = 0.04$) in the UW versus the EuroCollins groups, respectively.[48]

Both the EuroCollins and the UW are potassium-containing and hyperosmolar solutions. The UW solution contains lactobionate, raffinose, and hydroxyethyl starch as osmotic agents and other components including glutathione, adenosine, and the free-radical scavenger allopurinol. While the UW solution has a higher viscosity compared to the EuroCollins solution, which can potentially impede a sufficient initial flush, its glutathione content may serve to facilitate the regeneration of cellular adenosine triphosphate (ATP) and maintain membrane integrity and adenosine may provide the substrate for ATP regeneration during reperfusion. Newer solutions with increasing chemical stability, lower potassium content, and lower viscosity are in the investigational phase.

The Histidine-Tryptophan-Ketoglutarate Solution

The histidine-tryptophan-ketoglutarate (HTK) solution was first introduced in the 1970s as a cardioplegic solution in open heart surgery.[49] The HTK solution is increasingly being used by some centers as a preservation solution for kidneys. Tryptophan serves as a membrane stabilizer and antioxidant, whereas ketoglutarate acts as a substrate for anaerobic metabolism during preservation. The HKT has a low viscosity and contains less potassium and a strong histidine buffer that increases the osmotic effect of mannitol. The low viscosity of the HKT solution requires a large infusion volume at low flow rates to achieve complete tissue equilibrium.[17] An early European multicenter randomized prospective trial comparing the HTK with the UW solution in kidney preservation demonstrated similar incidence of DGF (33% vs. 33%) and allograft survival.[50] Studies comparing the HTK with the UW solution in deceased donor kidneys with cold ischemia time (CIT) greater than 24 hours have yielded conflicting results. A single-center study reported inferior outcome of deceased donor kidneys preserved for more than 24 hours in the HTK compared with the UW solution.[51] Whereas the incidence of DGF was comparable between kidneys preserved for less than 24 hours in the HTK or the UW solutions, this rate significantly increased to 50% in the HTK compared with 23.9% in the UW-preserved kidneys ($p = 0.006$) (DGF was defined as the need for hemodialysis within the first week posttransplant or oliguria—i.e., less than 0.5 L in 24 hours). In contrast, in another single-center study comparing the HTK and UW solutions in prolonged cold preservation of kidney allografts (CIT > 24 hrs), Agarwal and colleagues[52] demonstrated a lower incidence of DGF (16% vs. 56%, HTK and UW, respectively; $p = 0.005$) and a trend toward improved graft survival in the HTK cohort (DGF was restricted to the need for dialysis within the first postoperative week). The difference in the definition of DGF would preclude direct comparison of the conflicting results between the two studies. Large, randomized, blind studies are needed.

Currently, the UW solution is considered the gold standard preservation solution for kidney, liver, pancreas, and small bowel in the United States, whereas the HTK solution is the preservation solution of preference in Europe.

Pulsatile Machine Perfusion

Pulsatile hypothermic machine perfusion was first developed by Belzer in the late 1960s and used by many centers to preserve kidneys until the introduction of the EuroCollins preservation solution in 1969, when the practice declined. Over the last half decade, there has been renewed interest in the use of machine perfusion (MP) due to its reported beneficial effects in lowering the incidence of DGF and improvement in early and long-term allograft function.[53–54] and its ability

to provide metabolic support during perfusion. A metaanalysis on the effectiveness of MP versus cold storage demonstrated that MP led to a 20% reduction in the incidence of DGF in both heart beating and DCD kidneys compared with cold storage.[55] There was no statistically significant difference in 1-year graft survival between the two preservation methods. However, predictions based on quantifying the link between DGF and graft survival suggest potential improvements in graft survival of approximately 0% to 6% at 10 years. Whether MP might prove to be superior to cold storage awaits further studies. Nonetheless, MP may permit identification of kidneys that will likely result in primary nonfunction, thus sparing a recipient the morbidity associated with the transplant operation and the potential for the development of allosensitization.[53] In this respect, pulsatile perfusion of kidneys may aid in optimizing the use of marginal kidneys. Currently, the perfusion index (PFI) is used to assess whether an organ must be discarded. The possibility of using different PFI thresholds for single and dual organ transplantation is being explored.

Prevention Using Drug Therapy

In order to minimize the incidence and severity of ATN, the use of various pharmaceutical agents and immunosuppression protocol modifications have been advocated to promote postoperative diuresis or avoid early postoperative use of vasoconstrictive calcineurin inhibitors or both.[56] The use of diuretics is discussed in the management section. Some programs use routine induction therapy with antilymphocyte agents in all patients, thereby obviating the use of renovasoconstricting CNI, cyclosporine, or tacrolimus. More commonly, however, induction therapy is only used selectively in patients with anticipated or established DGF. As ATN may render the allograft more susceptible to immunological injury, the use of antilymphocyte antibodies in this setting may also be beneficial due to their potent immunosuppressive effect. Intraoperative thymoglobulin administration has been reported to be associated with a significant decrease in DGF and better early allograft function compared to postoperative administration, presumably through modulation and attenuation of graft ischemia-reperfusion injury.[57]

Mannitol administration before the release of vascular clamps has been suggested to reduce the risk of postoperative ATN. Dopamine infusions at low levels of 1 to 5 mcg/kg/min are used routinely at some centers to promote renal blood flow and to counteract cyclosporine-induced renal vasoconstriction.[56] The benefits of dopamine have not been proved in randomized trials, and its use is largely institution dependent. Fenoldopam, a selective agonist of dopamine-1-receptors with both systemic and renal vasodilator properties, has been suggested to have potential nephroprotective effects. In stable renal transplant recipient, fenoldopam has been shown to reverse cyclosporine-mediated renal vasoconstriction.[58]

Anecdotal reports comparing low "renal dose" dopamine to fenoldopam mesylate to prevent ischemia-reperfusion injury in renal transplantation showed no statistically significant difference in urine output, renal vascular resistive index, BUN, or creatinine on postoperative day 1, but did show a trend favoring the fenoldopam group.[59] Studies in critically ill patients in nontransplant settings suggest that fenoldopam is more effective than low-dose dopamine in reversing renal hypoperfusion associated with acute early renal dysfunction.[60] However, whether the effects of fenoldopam or dopamine in native kidneys can be extrapolated to a denervated renal allograft is currently not known. The role of fenoldopam in reducing the incidence or severity of posttransplant DGF remains to be defined.

Administration of calcium channel blockers (CCB) to the donor or recipient, or at the time of vasculature anastomosis, is routinely used in many transplant centers largely as a result of randomized clinical trials showing improved initial function with their use.[61] The presumed mechanism of action is by virtue of a direct vasodilatory effect. The kidney is often observed to "pink up" when verapamil is injected into the renal artery during surgery.[45] A Cochrane metaanalysis of peritransplant CCB use for the prevention of ATN in "at risk" de novo kidney transplant recipients involving 13 randomized controlled trials demonstrated a beneficial effect of CCB in lowering the incidence of ATN (relative risk [RR] 0.62, 95% confidence interval [CI] 0.46 to 0.85) and DGF (RR 0.55, 95% CI 0.42 to 0.73) compared to controls. However, there was no difference between control and treatment groups in terms of graft loss, mortality, or dialysis requirement.[62] In one single-center study, Boom and colleagues[63] demonstrated that serum calcium levels correlated with an increased incidence of DGF independent of the presence of microscopic nephrocalcinosis, and the use of perioperative CCBs was shown to have a protective effect.

Whether the use of dopamine, CCBs or fenodolpam confers a beneficial effect on long-term allograft function and/or graft survival beyond their vasodilatory effect and improvement in renal blood flow in the perioperative period remains to be defined. Large, multicenter, randomized, controlled trials are lacking.

One single-center retrospective study suggested that perioperative ACE inhibitors or angiotensin II receptor blockers (ARB) therapy does not delay recovery of graft function, nor does it promote DGF. In contrast, significantly faster graft recovery was seen among ACEI- or ARB-treated patients with DGF ($p < 0.01$).[64] Although inhibition of the renin angiotensin aldosterone system might prove to be beneficial in patients with DGF, further recommendations on the routine use of ACEI and/or ARB in the immediate posttransplant period awaits large prospective randomized trials.

Although various pharmacological approaches to the treatment of renal ischemia-reperfusion injury have shown promising results in experimental animal models, they have not proved successful in clinical settings. Randomized trials of allopurinol and other oxygen-free radicals scavengers have not shown convincing benefit in graft function.[65] Although prostaglandins have been shown in animal models to minimize ischemic injury,[66] no benefit was found in a blinded trial of the prostaglandin E analogue enisoprost.[67] Similarly, although pretreatment with an antibody preparation against the intracellular adhesion molecule 1 (anti-ICAM-1) has been shown in experimental rat models to alleviate ischemic reperfusion injury, no benefit was found in a randomized multicenter trial of anti-ICAM-1 monoclonal antibody enlinomab.[68] Blinded trials of atrial natriuretic factor administration have shown only marginal benefit in native kidney ATN.[69] In renal transplant recipients with DGF, it has been shown that neither renal vasoconstriction nor hypofiltration

is alleviated by a progressive elevation of endogenous plasma atrial natriuretic peptide levels,[70] and it is unlikely that this agent will find a place in the transplant setting.

Current Investigational Agents

Carbon Monoxide

Carbon monoxide (CO), a product of heme metabolism by heme oxygenases (HO-1, HO-2, HO-3) is known to be toxic at high concentrations due to its ability to interfere with oxygen delivery. However, at low concentrations, CO has been shown to have cytoprotective effect through its antiinflammatory, vasodilating, and antiapoptotic properties.[71] Experimental studies in rat transplant models have shown that inhalation of low-dose CO was effective in inhibiting ischemia/reperfusion injury-induced activation of proinflammatory mediators, neutrophil extravasation, and apoptosis, and improvement in allograft function.[71] Its use has also been suggested to prevent the development of chronic allograft nephropathy (CAN) in a rat model of kidney transplantation. Renal allograft function in air-controls progressively deteriorated with substantial proteinuria, whereas CO-treated grafts had significantly better creatinine clearance with minimal proteinuria.

In air-exposed grafts, histological examination demonstrated the development of progressive CAN. In contrast, CO-treated grafts had minimal tubular atrophy and interstitial fibrosis, with negligible collagen IV deposition. In vitro analyses revealed that CO-treated recipients had significantly less T-cell proliferation against donor peptides via the indirect allorecognition pathway and less antidonor immunoglobulin G (IgG) antibodies compared to air controls. Intragraft levels of mRNA levels for chemokines, IL-2, and ICAM-1 were significantly decreased in CO-treated than in air-treated allografts. Furthermore, reduction of blood flow in air-treated grafts was prevented with CO treatment.[72]

The use of kidneys retrieved from CO-poisoned donors have resulted in variable and conflicting results. Postal survey of transplant centers and intensive care units revealed that of the 14 transplant recipients of CO-poisoned donors, six had normal renal function.[73] Anecdotal case reports revealed unexpectedly good allograft outcome despite prolonged warm ischemia time (100 minutes). The patient had immediate graft function with steady decline in serum creatinine and excellent allograft function at 1-month follow-up (serum creatinine <1.0 mg/dl). It is speculated that the favorable outcome despite prolonged warm ischemia time might have been related to the previous exposure of CO in the donor.[74] Whether exposure of the brain-dead donor to low-dose CO might prove to be beneficial in the preservation of donor organs is a subject of ongoing research.

P53 Inhibitor

Analysis of gene expression in rat isografts from brain-dead donors demonstrated that p53 is activated upon brain death in organ donors and during acute tubular injury that occurs following renal transplantation, leading to the induction of apoptosis and cell death.[75] In contrast, inhibition of p53 in a rat model of ischemia/reperfusion injury has been shown to prevent apoptosis and protect renal function when given up to 14 hours after the ischemic insult.[76] It is hypothesized that p53 can be a target candidate for intervention in ischemia/reperfusion-mediated acute kidney injury. I5NP is a nuclease-resistant, synthetic double-stranded oligonucleotide designed to temporarily inhibit the expression of the proapoptotic gene p53. It is being developed for the prevention of acute kidney injury in high-risk patients undergoing major cardiovascular surgery and in the prophylaxis of DGF after renal transplantation. A multicenter, prospective, controlled, randomized, double-blind phase I/II dose escalating study to evaluate the safety, pharmacokinetic, and clinical activity of I5NP for the prophylaxis of DGF in recipients of deceased donor kidneys who are at risk for DGF is currently underway. The latter is defined as ECD, DCD or standard criteria donor with cold ischemia time of greater than 24 hours.

MANAGEMENT OF DELAYED GRAFT FUNCTION

The differential diagnosis of DGF (see Table 37-2) must be considered before a patient is labeled with posttransplant ATN. Most patients with DGF are oliguric or anuric. Knowledge of the patient's native urine output is critical to assess the origin of the early posttransplant urine output. From the previous discussion of the etiology of DGF, it is clear that information about the donor kidney itself is critical. When the transplant is from a living donor, postoperative oliguria is rare because of the short ischemia time. Nonetheless, if postoperative oliguria does occur, complications with allograft vascularization must be immediately considered. In contrast, when a patient receives a deceased donor kidney from a nonideal donor, DGF may be anticipated. The mate kidney from a deceased donor often behaves in a similar manner, and information on its function can be useful.[1]

Anuria refers to negligible urine production. Oliguria in the peritransplant period typically refers to a urine output of less than about 50 ml/hr. Before the patient is submitted to a full evaluation for poor urine output, his or her volume status and fluid balance and patency of the Foley catheter must be assessed. If clots are present, the catheter should be removed while gentle suction is applied in an attempt to capture the offending clot. Thereafter, replacement with a larger catheter may be required. If the Foley catheter is patent and the patient is clearly hypervolemic, up to 200 mg of furosemide may be given intravenously. If the patient is judged to be hypovolemic or if a confident clinical assessment cannot be made, a judicious trial of isotonic saline infusion may be given, with or without subsequent administration of furosemide as dictated by the patient's response to saline infusion alone. A suggested algorithmic approach to postoperative fluid management in an olguric patient is shown in Figure 37-2.

Indications for dialysis in the transplant recipient with DGF are essentially the same as in any patient with postoperative renal dysfunction. Hyperkalemia is a persistent danger and must be monitored repeatedly and treated aggressively. It is usually safest to dialyze patient once the potassium level is above 5.5 mg/dl. Other treatment modalities, such as intravenous calcium and glucose with insulin, are valuable temporizing measures but do not obviate the need

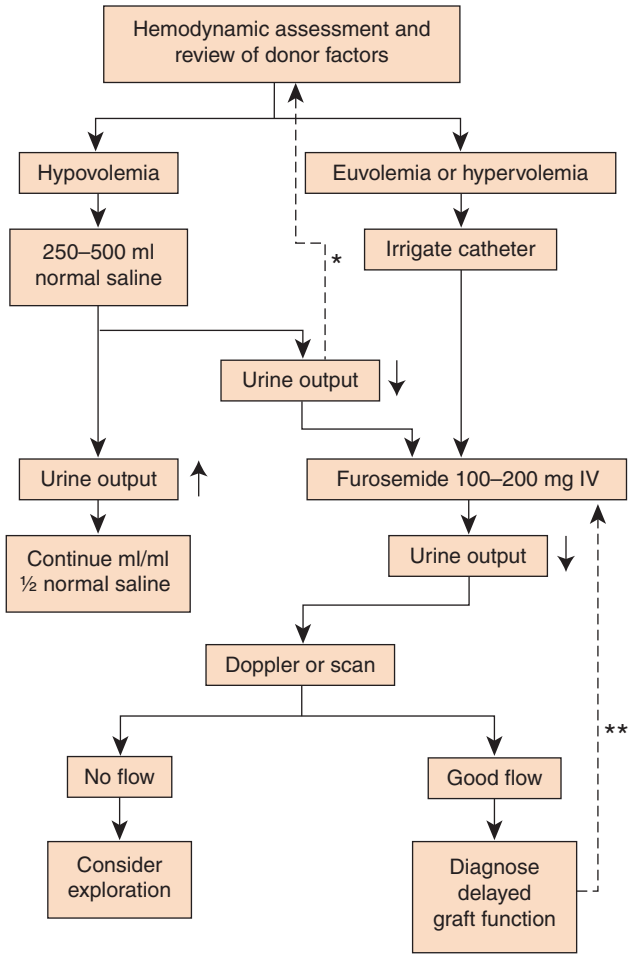


FIGURE 37-2 Algorithmic approach to posttransplant oliguria. *The volume challenge can be repeated but only after careful reassessment of the volume status and fluid balance.
**Repeated doses of intravenous furosemide or furosemide drips may be valuable in patients whose urine output fluctuates.

for dialysis. Sodium polystyrene sulfonate (Kayexalate) should not be administered rectally in the early posttransplant period because it may induce colonic dilatation and predispose to perforation.[77]

Patients with DGF often become volume overloaded in the early posttransplant period because they are frequently subjected to repeated volume challenges. It is not infrequent for such patients to gain several kilograms of fluid over their dialysis dry weight. Ultrafiltration with or without dialysis may be required. When dialyzing posttransplantation patients who have DGF, care must be taken to avoid hypotension, which may perpetuate graft dysfunction. A bicarbonate dialysate and biocompatible dialyzer should be used. In patients with established DGF, the dialysis requirement should be assessed daily until graft function improves.

DIAGNOSTIC STUDIES IN PERSISTENT OLIGURIA OR ANURIA

Failure to respond to volume challenge and furosemide administration warrants further evaluation with diagnostic imaging studies to determine the cause of the early posttransplant oliguric state. The urgency of this evaluation partially depends on specific clinical circumstances. If diuresis is expected following an uncomplicated living donor kidney transplantation and oliguria occurs, diagnostic studies should be performed immediately—in the recovery room if necessary. In contrast, if oliguria is anticipated following an ECD kidney transplantation, studies can usually be safely delayed by several hours.

Diagnostic studies are used to confirm the presence of blood flow to the graft and the absence of a urine leak or obstruction. Blood flow studies are performed scintigraphically or by Doppler ultrasound.[78] The typical scintigraphic finding in ATN is relatively good flow to the graft but with poor excretion. If the flow study reveals no demonstrable blood flow, a prompt surgical reexploration is necessary to attempt to repair any vascular technical problem and diagnose hyperacute rejection. These kidneys are usually not salvageable, however, and are removed during the second surgery. If adequate blood flow is visible in the scintiscan or Doppler studies, the possibility of ureteral obstruction or urinary leak needs to be considered and can be evaluated by the same imaging studies. In the first 24 hours after transplantation, as long as the Foley catheter has been providing good bladder drainage, the obstruction or leak is almost always at the ureterovesical junction and represents a technical problem that needs surgical correction.[45]

OTHER CAUSES OF GRAFT DYSFUNCTION DURING THE FIRST WEEK AFTER TRANSPLANTATION

Early Acute Rejection

Hyperacute Rejection

Rejection occurring immediately after transplantation or hyperacute rejection is due to presensitization and is mediated by antibodies to donor human leukocyte antigens (HLA). The rejection occurs after an amnestic response where a critical level of antibodies is produced and results in an irreversible vascular rejection. Hyperacute rejection may be evident before wound closure or "hidden," only to manifest itself as primary nonfunction of the kidney allograft.[79] Patients are usually anuric or oliguric and often febrile with associated graft tenderness. The renal scan shows little or no uptake, a finding that differentiates this cause of graft dysfunction from the much more frequent ATN. There may be evidence of intravascular coagulation. Prompt surgical exploration of the allograft is often indicated, and when in doubt, an intraoperative biopsy is performed to determine viability. Because of assiduous attention to the pretransplantation crossmatch, it occurs rarely in modern transplantation practice.

Because hyperacute rejection is due to preformed antibodies, it is characterized morphologically by arterial and glomerular thrombi, which often contain neutrophils or may have accumulation of intravascular neutrophils as the initial event. The interstitium is edematous and variable parenchymal necrosis or infarction is observed, depending on the length of time from thrombosis to nephrectomy. There is no significant vascular or tubulointerstitial inflammation. Immunofluorescence microscopy reveals fibrin within the

intravascular thrombi, and IgM, IgG, C3, and fibrin may be found in arterial and capillary lumina, or lining or within the intimas.[80] In this setting, most allografts need to be removed.

Accelerated Acute Rejection

Accelerated acute rejection or delayed hyperacute rejection occurs within 24 hours to a few days after transplantation and may involve both antibody-mediated and cellular immune mechanisms. Accelerated acute rejection probably represents a delayed amnestic response to prior sensitization and may be seen after donor-specific transfusions in recipients of living-donor transplant due to a primed T-cell response.[81] HLA sensitization through repeat transplants, multiple pregnancies, or multiple transfusions are well-substantiated risk factors for hyperacute or accelerated acute rejection. However, with the current sensitive crossmatching techniques such as flow cytometry or antihuman globulin augmentation tests and the more recent availability of the luminex bead-based assays,[82,83] hyperacute rejection has virtually been nonexistent (discussion of various crossmatching techniques is beyond the scope of this chapter).

Early Cell-Mediated Acute Rejection

Early cell-mediated rejection, with a typical interstitial infiltrate or endarteritis, can also be detected in the latter part of the first week after transplantation, although it typically occurs somewhat later. It may develop in an allograft already suffering from ATN and may be difficult to recognize clinically because the patient is anuric or oliguric. An allograft with DGF, presumably due to ATN, should undergo serial biopsies at intervals of about 10 days to detect the covert development of rejection. The prognosis for long-term function of these grafts is poor, although adequate function may be achieved, if the ATN reverses and the rejection responds to intensification of immunosuppression (see Chapters 29 and 30).

Nonimmunological Causes

Nonimmunological causes of DGF (other than ATN) may occur in the first posttransplant week or any time thereafter and are discussed under Graft Dysfunction in the Early Posttransplant Period.

Long-Term Impact of Delayed Graft Function

Studies on the impact of DGF on long-term graft function have yielded conflicting results.[6,8,84,85] Data from the UNOS Scientific Renal Transplant Registry revealed that DGF reduced 1-year graft survival from 91% to 75% ($p < 0.001$) and graft half-life from 12.9 to 8 years, independent of early acute rejection. The deleterious effect of DGF with or without acute rejection on graft half-life remained significant after adjusting for discharge serum creatinine less than 2.5 mg/dl. Interestingly, in the presence of DGF with or without acute rejection, the survival advantage of well-matched kidneys (0-1 mismatch) over those of poorly matched (5-6 mismatch) kidneys was no longer seen.[84] Some group of investigators showed that DGF, when combined with rejection, had an additive adverse effect on allograft survival, whereas others suggested that DGF is deleterious to graft outcome only when associated with reduced renal mass and hyperfiltration injury.[85,86]

The harmful effect of DGF may also be more pronounced when marginal donor kidneys are used. It should be noted that in most studies reported transplant biopsies were not performed and DGF was presumed to be due to ATN. This, along with the lack of universally defined criteria for DGF and the difference in donor and recipient characteristics, may explain, in part, conflicting results among various studies. In addition, the duration of DGF has also been suggested to have an adverse impact on graft survival.[87,88] Yokohama and colleagues[88] reported a higher incidence of graft failure in those with prolonged delayed recovery of graft function. Five-year graft survival for those with immediate graft function compared to those with DGF lasting 8 days or less, and those with DGF lasting for more than 8 days were 89%, 85%, and 50%, respectively.[88] Similarly, others have reported that DGF lasting more than 6 days is associated with decreased long-term graft survival.[87]

Graft Dysfunction in the Early Posttransplant Period

The early posttransplant period usually refers to the time span following discharge from the hospital until the second or third month, the time when most patients have achieved stable graft function and immunosuppressive regimen. Although the differentiation between early and late posttransplantation is clearly somewhat arbitrary, it is based on the finding that most acute rejection episodes occur within the first few months. Similarly, most episodes of cyclosporine or tacrolimus toxicity occur during this period, as do most cases of surgery-related graft dysfunction.

By the second week, graft function of most patients with DGF due to ATN begins to improve, although some patients remain oliguric for several weeks. In all patients who have become independent from dialysis, measurement of serum creatinine (SCr) concentration is a simple and widely available test but is an invaluable marker of kidney transplant function that greatly facilitates posttransplant management. In clinical transplantation practice, it is generally not necessary to measure renal function by more accurate and sophisticated techniques, such as creatinine clearance and isotope filtration rates, although these techniques may be valuable in assessing the significance of changes in SCr with time and in providing a more accurate baseline value for follow-up. The level of SCr reached by the second week is an important determinant of long-term graft function; any baseline greater than 2 mg/dl is a source of concern necessitating evaluation. The relationship between SCr and adverse outcome in renal transplantation remains the most robust predictor of graft survival at all time points.[2] Analysis of the UNOS database involving 105,742 adult transplant recipients performed between 1988 and 1998 revealed that posttransplant serum creatinine greater than 1.5 mg/dl at 1 year

significantly decreased graft half-life regardless of any episode of acute rejection (discussed in further details under Graft Dysfunction in the Long-Term Follow-Up).[89]

Elevations in SCr greater than 25% from baseline almost always indicate a significant and potentially graft-endangering event. Smaller elevations may represent laboratory variability; nonetheless, it is advisable that the level be repeated within 48 hours. The clinical algorithm in approaching SCr elevations (or failure to reach a low baseline value) is similar, in principle, to that used in the nontransplant setting: "prerenal," "renal," and "postrenal" causes need to be considered. In the early posttransplantation period, acute rejection and nephrotoxicity are constant threats to graft function. In addition, anatomical or surgical problems must also be considered before medical diagnoses are sought to explain deteriorating graft function.

ACUTE REJECTION

Clinical Presentation

Acute rejection is the term conventionally used to describe the cellular immune response to the transplant that produces enough inflammation and destruction to cause recognizable graft dysfunction, as indicated by an elevation in SCr. It is now clear that humoral alloreactivity can also cause direct graft injury and acute allograft dysfunction (discussed in further details in a later section). Although using the SCr to define the occurrence of rejection is highly convenient, it is insensitive in detecting subclinical pathogenic allograft inflammation or "subclinical rejection." Fifteen to 80% protocol biopsies performed in the first 3-6 months posttransplant in patients with well-functioning grafts have been reported to show histopathological lesions of acute rejection.[90,91] Early reports suggested that untreated subclinical rejection is a precursor to chronic rejection and chronic allograft nephropathy.[87–92] Nonetheless, treatment of subclinical rejection has not been consistently shown to prevent late clinical rejections and/or the development of chronic rejection or fibrosis in serial biopsies.[93–95] Controlled trials documenting the beneficial effect of treating subclinical rejection are lacking. More recently, it has been suggested that the presence of a higher proportion of FoxP3$^+$ T regulatory cell (Treg) within the global T-cell infiltrate may facilitate renal engraftment.[91] Hence, immunostaining for FoxP3+Treg in patients with subclinical rejection might be useful in identifying a subset of patients in whom intensification of immunosuppression is not indicated. Further studies are needed.

The classic signs and symptoms of acute rejection are fever, malaise, graft tenderness, and oliguria. Acute rejection can present with a seemingly innocuous influenza like illness, and transplant recipients should be warned of the potential significance of these symptoms. These symptoms consistently and rapidly resolve when the rejecting patient receives pulse steroids, presumably as a result of the blockade of IL-1 by corticosteroids.[96] Since the advent of cyclosporine and other potent immunosuppressive agents, the classic clinical signs and symptoms of acute rejection are seen less frequently; many rejections only present as asymptomatic elevations in SCr. Therefore, a search for alternative causes of graft dysfunction is warranted in patients who present with fever, graft tenderness, and/or oliguria.

Fever may indicate either rejection or infection and should never be presumed to be due to the former without considering the latter. The sources of infection during the first few weeks typically involve bacterial pathogens in the surgical site, urinary tract, or respiratory tract. In more severe cases of infections, the SCr may be elevated due to systemic vasodilatation.[97] Because infections may have similar presentations as acute rejections, a thorough history, physical exam, standard laboratory tests, and a chest radiograph must be obtained prior to the diagnosis and treatment of rejection. An elevated white blood count is frequently seen in the posttransplant period, particularly in patients still receiving a high baseline dose of corticosteroids, and is often unhelpful in the differential diagnosis. Fever due to infection with opportunistic infections usually does not occur in renal transplant recipients until several weeks after transplantation. Cytomegalovirus infection may mimic acute rejection and must always be considered, particularly in CMV-negative recipients of kidneys from CMV-positive donors.[97] Over the past decade, polyoma BK virus infection has emerged as an important cause of acute and chronic allograft dysfunction and graft loss in renal transplant recipients. Various degrees of inflammation and focal tubulitis may be seen on allograft biopsy, mimicking acute rejection (discussed in further details under Graft Dysfunction During Long-Term Follow-Up).

Many patients comment about incisional tenderness in the first few days and can be reassured that this is of little clinical significance. The new onset of graft tenderness in a previously pain-free patient, however, is a significant symptom that needs to be evaluated. A tender, swollen graft in a patient with a rising SCr concentration and fever usually indicate rejection, although the possibility of acute pyelonephritis must also be considered.[97] Cyclosporine and tacrolimus toxicity and CMV or BK infection do not produce graft tenderness. Excruciating localized perinephric pain is usually a result of a urine leak.[98]

Both rejection and cyclosporine toxicity may produce weight gain and edema as a result of impaired graft function and avid tubular sodium reabsorption. Mild peripheral edema is common in stable patients receiving cyclosporine. The proliferation signal inhibitor sirolimus can exacerbate CNI nephrotoxicity and/or cause mild or refractory peripheral edema. The latter generally resolves with discontinuation of the offending agent. Acute rejection, cyclosporine, and tacrolimus toxicity can all produce graft dysfunction in the absence of oliguria. Oliguria is common in severe acute rejection; its occurrence makes the diagnosis of drug toxicity less likely and the necessity to exclude an anatomical cause all the more critical.

IMAGING STUDIES

The morphological findings in acute rejection are nonspecific and somewhat subjective. Nonetheless, imaging studies are performed to exclude alternative causes of graft dysfunction. In mild acute rejection episodes, ultrasonographic and nuclear medicine study results may be normal.[20,78] Ultrasonographic abnormalities include graft enlargement, obscured

corticomedullary definition, prominent hypoechoic medullary pyramids, decreased echogenicity of the renal sinus, thickened uroepithelium, and scattered heterogenous areas of increased echogenecity. The resistive index is also elevated, as in other causes of graft dysfunction that result in increased intrarenal vascular resistance.

Acute rejection may appear on nuclear medicine technetium 99m DTPA and MAG-3 scans as delayed visualization (decreased perfusion) of the transplant in the first-pass renal scintiangiogram.[78] Poor parenchymal uptake with high background activity (poor kidney function and clearance) may be seen in the second and third phases of the three-phase imaging study. However, it should be noted that neither renal Doppler ultrasound nor radioisotope flow scan is sufficiently sensitive or specific in the diagnosis of acute rejection. Although invasive, tissue diagnosis remains the most accurate means of differentiating acute rejection from other causes of acute deterioration of allograft function.

HISTOPATHOLOGICAL DIAGNOSIS

Percutaneous renal biopsy is the gold standard diagnostic tool for acute rejection. The timing and frequency of kidney biopsies vary among centers. One clinical approach to graft dysfunction is to base therapeutic intervention empirically on the clinical presentation and laboratory values. A favorable response confirms the diagnosis, but a lack of response requires tissue diagnosis. It is probably wise to obtain tissue diagnosis of rejection before embarking on a course of lymphocyte-depleting antibodies such as OKT3 or antithymocyte globulin (Thymoglobulin) because occasionally CMV infection may present as fever and graft dysfunction,[97] in which case potent immunosuppressive therapy could be catastrophic. Furthermore, the diagnosis of acute antibody-mediated rejection relies on the pathological finding of C4d deposition in peritubular capillaries. A more aggressive approach to graft dysfunction is to perform a kidney biopsy whenever the SCr level rises 25% over the baseline value.

TYPES OF ACUTE REJECTION

Acute rejections occur, most typically, between the first week and the first few months after transplantation. In unsensitized patients with low levels of preformed antibodies, acute rejections rarely occur in the first week, while very early rejections or accelerated acute rejection may occur in sensitized patients (as previously described). In recent years, various desensitization protocols have allowed successful transplantation in highly sensitized renal transplant candidates (discussion is beyond the scope of this chapter). On the basis of the underlying immunopathogenic mechanisms, acute rejection can be divided into cell-mediated and antibody-mediated. Approximately 90% of acute rejection episodes are predominantly cell-mediated, whereas 12% to 37% of all acute rejection episodes have a humoral component.[99,100] The histological diagnostic criteria are different for these two types of rejection and are discussed separately. It should be noted, however, that the histopathological findings of acute cellular rejection and acute antibody-mediated rejection may occur in a renal biopsy simultaneously.

Acute Cellular Rejection

Acute cellular rejection generally occurs after the first posttransplant week and most commonly within 3 months after transplantation. It has been suggested that $CD4^+$ T-cells play an important role in the initiation of rejection, whereas $CD8^+$ T-cells are critical at a later stage.[81] Over the last decade, gene analysis using molecular biology techniques such as reverse transcription-polymerase chain reaction (PCR) has been suggested to provide a noninvasive diagnostic tool in the diagnosis of acute rejection. Elevated peripheral blood and/or urine levels of perforin, granzyme B, fas-ligand, and serpin proteinase inhibitor-9 have variably been reported to indicate the presence of ongoing acute rejection.[101] Independent investigators have suggested that measurement of urine perforin mRNA and granzyme B messenger RNA may offer a noninvasive means of diagnosing acute renal allograft rejection with a sensitivity of 79% to 83% and a specificity of 77% to 83%.[102] In one single-center study, perforin and granzyme B had sensitivities of 50% and specificities of 95% in predicting rejection when a cutoff value of 140 was used.[103] Whether measurement of these cytotoxic proteins may be beneficial in the diagnosis of acute cellular rejection remains to be confirmed.

More recently, it has been suggested that CD4 + CD25 + FoxP3 regulatory T-cells (Treg) are involved in the maintenance of immune homeostasis and tolerance to self and nonself antigens.[104] Single-center study in renal transplant recipients with DGF suggested that measurement of FOXP3 gene (X-linked forkhead/winged helix transcription factor) in peripheral blood leukocytes and urinary cells provides an accurate marker of acute rejection with a reported sensitivity, specificity, positive and negative predictive values, and accuracy between 94 and 100%.[101] In a single-center case-control study consisting of stable renal transplant recipients undergoing tacrolimus dose reduction at month 4 and complete withdrawal at month 6, Kreijveld and colleagues[105] demonstrated that prior to tacrolimus dose reduction, the ratio between $CD8^+$ T-cells and Treg was higher in rejectors compared to nonrejectors. Rejectors also had a higher ratio between memory $CD4^+$ T-cells and Treg, and ratios less than 20 were only observed in nonrejectors. In rejectors, an increase over time was observed in the percentage of naïve T-cells in the peripheral blood, with a reciprocal decrease in the percentage of effector T-cells. Although more pronounced for $CD4^+$ T-cells, this phenomenon was also observed for $CD8^+$ T-cells. Whether the combination of the memory T-cells: Treg ratio and the changes in T-cell subsets over time might prove useful in the detection of acute rejection remains to be studied. The use of immune monitoring as a noninvasive tool in the prediction and/or diagnosis of acute rejection is a subject of intense, ongoing research.

Acute Antibody-Mediated Rejection

Acute antibody-mediated rejection (AMR) occurs within the first 1 to 3 weeks after transplantation and has been reported to occur in 5%-7% of renal transplant recipients and 12%-37% of biopsies taken for acute rejection.[100] In a National Conference to assess AMR in solid organ transplantation, it has been suggested by experts in the field that the

TABLE 37-7 Diagnostic Criteria of Acute Antibody-Mediated Rejection after Kidney Transplantation

Clinical evidence of graft dysfunction	
Histological evidence of tissue injury	*ATN/macrophages/ thrombi in capillaries* +/*or fibrinoid necrosis* +/*or acute tubular injury*
Immunopathological evidence for antibody action	*C4d in PTC or Ig/ C3 in arteries*
Serological evidence of anti-HLA or other antidonor antibody at the time of biopsy	

diagnosis of acute AMR should require graft dysfunction to distinguish clinical from subclinical rejection.[106] The diagnosis of AMR also requires detection of the complement component C4d in peritubular capillaries and evidence of renal parenchymal injury (Table 37-7).[106] These may occur with or without features of ACR. However, it has been reported that C4d can be identified in allograft biopsies lacking morphological evidence of rejection. Furthermore, non-HLA and/or non-ABO antibodies along with antibody-independent mechanisms may theoretically result in C4d deposition, although this was not observed in ischemic or ischemia-reperfusion injury in perioperative renal transplant biopsies.[107]

The final requisite diagnostic element is serological evidence of antidonor (either anti-HLA or anti-ABO) antibody. The 2007 update Banff criteria suggested the inclusion of specific elements of AMR including peritubular capillaritis grading, C4d scoring, interpretation of C4d deposition without morphological evidence of active rejection, application of the Banff criteria to zero-time and protocol biopsies, and introduction of scoring for total interstitial inflammation (interested readers are referred to reference 106).

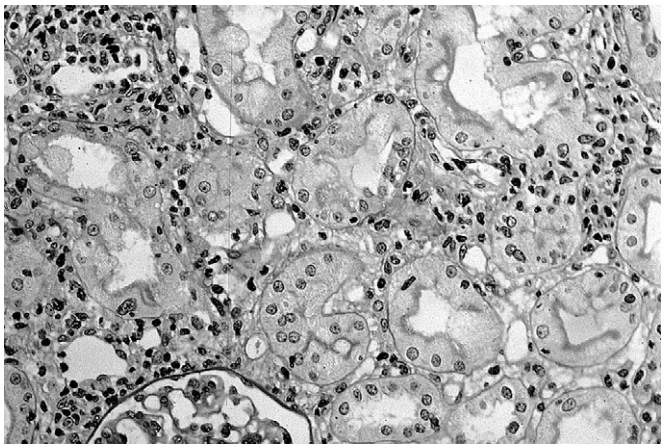


FIGURE 37-3 Acute cell-mediated tubulo-interstitial rejection. There are interstitial edema and lymphocytes, with lymphocytes in the walls of most tubules (tubulitis) (Periodic acid-Schiff × 300).

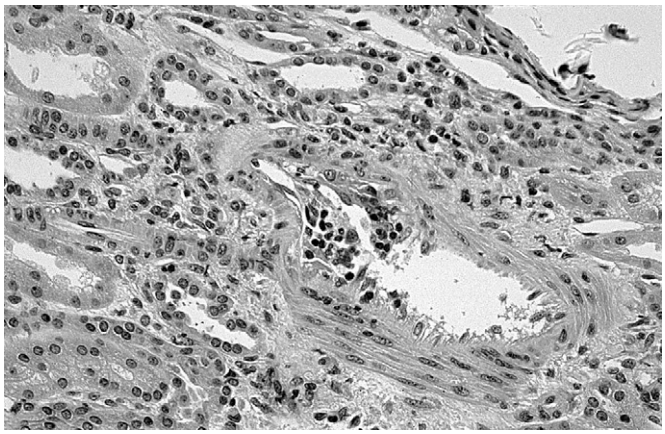


FIGURE 37-4 Acute cell-mediated vascular rejection. The artery contains swollen endothelial cells that are focally detached from the artery wall and undermined by lymphocytes. The adjacent interstitium has edema and a lymphocytic infiltrate (Periodic acid-Schiff × 350).

Core Biopsy

Biopsy evaluation for acute changes should be performed in unscarred portions of the renal cortex. Cell mediated acute rejection occurs as tubulointerstitial and vascular types. Cell-mediated tubulointerstitial acute rejection is characterized by lymphocytes in the walls of tubules (tubulitis) and may initially be found in distal tubules. There are associated interstitial edema and inflammation including lymphocytes, activated lymphocytes, monocytes, and occasional scattered eosinophils or plasma cells. Variable degrees of tubular cell flattening, necrosis, and regenerative change also are present (Figure 37-3). Vascular cell-mediated rejection involves small, and medium-sized arteries and arterioles and encompasses lymphocytes, monocytes, or both extending under the endothelial lining into the intima (endothelialitis or endarteritis), with endothelial cells appearing swollen and often detached from the vascular wall (Figure 37-4). Infrequently in severe cases, inflammatory cells are found in the arterial media and may be associated with smooth muscle cell necrosis;[108] neutrophils are not a component of cell mediated rejection. Vascular cellular rejection tends to be present focally and thus may be missed on biopsy. Therefore, a minimum of two arteries within the biopsy and at least seven slides of the tissue are required for an adequate assessment of vascular rejection.[109] Tubulointerstitial rejection usually accompanies the vascular form of cell mediated rejection, which may be associated with interstitial hemorrhage due to increased permeability of peritubular capillaries. The finding of interstitial hemorrhage suggests the presence of vascular rejection even in the absence of diagnostic arteries if other causes of hemorrhage, such as prior biopsy site and infarction, have been excluded.[110] In approximately 4% of biopsies demonstrating acute cell mediated rejection, glomeruli display a form of capillary rejection termed *acute transplant glomerulopathy*, in which capillary lumina contain many mononuclear leukocytes and swollen endothelial cells.[111] This must be differentiated from glomerular injury induced by antibody mediated rejection or CMV infection.

Antibody-mediated rejection (AMR), formerly termed *humoral rejection*, has as its hallmark the deposition of C4d around peritubular capillaries (PTC) in a linear pattern within the renal cortex or medulla.[112] C4d cannot be evaluated accurately in foci of necrosis or fibrosis, and is best demonstrated by immunofluorescence in frozen tissue sections, wherein at least 50% of the PTC have C4d in at least

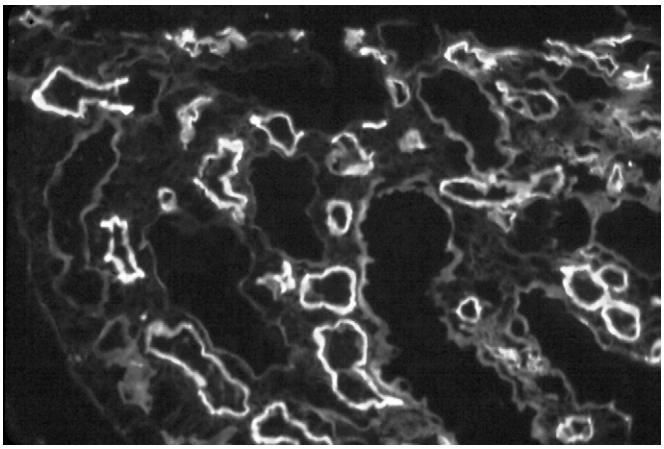


FIGURE 37-5 Acute antibody-mediated (humoral) rejection. There is bright staining of peritubular capillaries for C4d in a linear pattern (C4d immunofluorescence × 300).

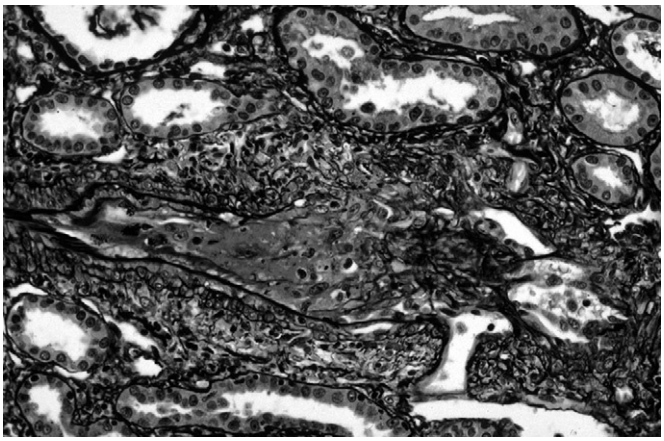


FIGURE 37-6 Acute antibody-mediated arterial rejection. The artery is thrombosed with transmural inflammation and leukocyte karyorrhexis (Periodic acid-methenamine silver × 250).

2+ intensity (on a scale of 0-4+) (Figure 37-5). Immunohistochemistry on paraffin embedded tissue also may be used, but is less sensitive with higher inter- and intraobserver variability.[113] In its classic form, AMR is a vascular process wherein neutrophils infiltrate artery walls associated with fibrin deposition and vascular wall fibrinoid necrosis, often accompanied by mononuclear leukocytes,[114] and with C4d in PTC (Figure 37-6). There may be accompanying intravascular thrombosis, glomerular inflammation, and foci of renal parenchymal necrosis or infarction. AMR also may occur as a microvascular form of injury associated with C4d deposition around PTC in the absence of arterial injury.[115] This may be associated with only minor tubular cell necrosis, with neutrophil infiltrates in the interstitium, tubules, and/or glomeruli, or with peritubular capillary thrombosis. Recently, monocytic infiltrates in glomeruli and PTC have been reported to be a manifestation of AMR, associated with C4d staining in PTC.[116] The currently suggested histological and immunopathological criteria for AMR are shown in Table 37-7. Infrequently, C4d may be found in PTC in the absence of tissue injury or other morphological or clinical features of AMR, particularly in ABO incompatible transplants; it has been suggested that this may indicate a state of graft accommodation, although this requires validation.[117]

The Banff Classification schema provides standardized morphological definitions of acute rejection, which undergo periodic revision to incorporate advances in the understanding of the morphology of rejection. The most recent iteration for acute allograft injury, reflecting findings from the Banff 2007 meeting, includes separate diagnostic categories for cell-mediated and antibody-mediated rejection with more distinction among the morphological features for each type of rejection.[106] AMR is listed as Category 2 rejection, which requires C4d staining in PTC and includes ATN-like (Type I), capillary and/or glomerular inflammation (Type II), and arterial (Type III) forms. A chronic active form of AMR also is recognized. In addition to the diagnosis, criteria are recommended in AMR for scoring C4d staining, grading the degree of peritubular capillaritis and scoring the degree of total interstitial inflammation. Banff Category 3 is the borderline category, characterized by foci of tubulitis and interstitial inflammation that fall short of the amount needed for a diagnosis of rejection (a minimum >25% of the interstitium to contain inflammation and >4 mononuclear leukocytes in a tubule). The significance of this category is uncertain; further study is required, possibly with the application of cytokine or gene analysis, to determine accurately the meaning of low-grade inflammation within the allograft.[118] Banff Category 4 now is termed *T-cell mediated rejection* and includes tubulointerstitial rejection (Types I A and B), vascular rejection with intimal arteritis (Types II A and B), and vascular rejection with transmural inflammation and smooth muscle necrosis (Type III). More than one form of rejection may be present simultaneously. Category 6 includes all other morphological findings associated with acute allograft failure such as ATN, infection, calcineurin inhibitor nephrotoxicity, and so on.

Cyclosporine and Tacrolimus Toxicity

Although biochemically distinct, cyclosporine and tacrolimus are two potent immunosuppressive agents with similar mechanisms of action and pathological patterns of nephrotoxicity. Their potential for impairment of graft function, particularly in the early posttransplant period, should be included in the differential diagnosis of the elevated serum creatinine level. It is important to note that there are various clinical and histological manifestations of cyclosporine and tacrolimus toxicity; in the early posttransplant period, the most important are the frequently occurring functional decrease in renal blood flow and GFR and the infrequently occurring thrombotic microangiopathy.

Functional Decrease in Renal Blood Flow and Filtration Rate

Cyclosporine and tacrolimus produce a dose-related, reversible, renal vasoconstriction that particularly affects the afferent arteriole. The glomerular capillary ultrafiltration coefficient (Kf) also falls, possibly because of increased mesangial cell contractility. Clinically, this condition is reminiscent of prerenal dysfunction, and in the acute phase,

tubular function is intact. The mechanism of the vasoconstriction is discussed in Chapter 38. Cyclosporine- and tacrolimus-induced renal vasoconstriction may manifest clinically as delayed recovery from ATN and as a transient, reversible, dose-dependent, and blood-level-dependent elevation in SCr concentration that may be difficult to distinguish from other causes of graft dysfunction.

Cyclosporine and Tacrolimus Blood Levels

The use of blood levels of cyclosporine and tacrolimus in clinical immunosuppressive management is discussed in Chapter 38. High blood levels of cyclosporine and tacrolimus do not preclude a diagnosis of rejection, although they may make it less likely, particularly in the case of tacrolimus. Nephrotoxicity may develop at apparently low levels of both drugs, and some degree of toxicity may be intrinsic to their use. Neprotoxicity and rejection may coexist. In clinical practice, particularly when SCr elevation is modest, it is fair to initially presume that a patient with a very high cyclosporine or tacrolimus level is probably suffering from nephrotoxicity and that a patient with deteriorating graft function and a very low drug level is probably undergoing rejection. If the appropriate clinical therapeutic response does not have a salutary effect on graft function, the clinical premise needs to be reconsidered. Cyclosporine toxicity usually resolves within 24 to 48 hours of a dose reduction, whereas tacrolimus toxicity may take longer to resolve. Progressive elevation of the plasma creatinine level, even in the face of persistently high drug levels, suggests rejection.

Patients may detect somatic manifestations of toxicity, and these symptoms may suggest the diagnosis. Tremor and headache are produced by both drugs and are particularly marked with tacrolimus. Compared to the original oil-based formulation of cyclosporine (Sandimmune), the Neoral formulation of cyclosporine produces higher peak levels and a more consistent pharmacokinetic profile with a magnified area under the curve (AUC) in some patients.[119] The high peak level may be detected by patients as headache and flushing, whereas the magnified AUC may predispose to nephrotoxicity at a time when trough levels are deemed not elevated.

Cyclosporine (CsA) dosing is traditionally based on trough blood levels (C0), although the area AUC correlates better with systemic drug exposure and posttransplantation clinical events. Mahalati and colleagues[120] were among the first to demonstrate that CsA concentration measured 2 hours after Neoral dose (C2) correlates better with both the AUC and the risk of acute rejection and cyclosporine nephrotoxicity compared to trough (C0) monitoring. Studies evaluating the clinical outcomes of C2 versus C0 monitoring have yielded variable results. In a retrospective analysis, the Canadian Neoral Renal Transplantation Study Group[121] demonstrated a significantly lower acute rejection rate in patients who achieved C2 levels of greater than 1500 mcg/L in the first 2 weeks after transplantation ($p < 0.001$). In contrast, results of a single-center randomized controlled study failed to demonstrate the advantage of C2 monitoring in the first 3 posttransplant weeks. The incidence of DGF, acute rejection rate at 3-month posttransplantation, and 1-year graft survival rate were comparable between the C0 and C2 groups.[122]

Limited single-center studies evaluating conversion of C0 to C2 monitoring in stable renal function suggested the beneficial effects of C2 monitoring in dyslipidemia and blood pressure control. Notably, conversion from C0 to C2 monitoring allowed significant cyclosporine dose reduction without an increase in the rejection rates. Renal allograft function has variably been reported to remain unchanged or improve in overexposed patients during short- and long-term follow-up.[123–126] Results of a prospective study consisting of 110 stable renal transplant recipients more than 12 months posttransplant suggested that conversion of maintenance C0 to C2 monitoring offers the clinical benefits of better control of hypertension and dyslipidemia with effective protection against chronic allograft dysfunction during a follow-up period of 40 ± 11 months.[126]

Large prospective randomized studies are still needed before adoption of C2 monitoring can be routinely recommended. Nonetheless, C2 monitoring is increasingly being used by many centers as a tool to monitor Neoral dose adjustments.

DRUG INTERACTIONS

Well-substantiated potentiation of renal impairment has been described when amphotericin, aminoglycosides, NSAIDS, ACE inhibitors, and/or angiotensin receptor antagonists are used in patients receiving CNI therapy. The proliferation signal inhibitors sirolimus and everolimus have been shown to be devoid of nephrotoxicity when used as base therapy without a CNI. However, in two Phase III clinical trials (The Global and US Rapamune Study Group), concomitant administration of cyclosporine and sirolimus has been shown to potentiate CsA nephrotoxicity.[127,128] There has been substantial evidence suggesting that CsA exposure is increased by a pharmacokinetic interaction with sirolimus. In rat animal models, sirolimus has also been shown to increase partitioning of CSA into renal tissue to a greater extent than in whole blood.[129] When combination therapy is used, a reduction in therapeutic CsA level is desirable, particularly when there is an unexplained rise in SCr level. Studies on the potential drug interaction between tacrolimus and sirolimus have yielded variable and even contradictory results. Coadministration of tacrolimus and sirolimus has been shown by some[130,131] but not by others[132] to result in reduced exposure to tacrolimus. Acute allograft failure following sirolimus-tacrolimus therapy has been reported.[133] Until further evidence becomes available, caution should be exercised when tacrolimus-sirolimus (or everolimus) combination therapy is used.

THROMBOTIC MICROANGIOPATHY

Although uncommon, the use of cyclosporine and tacrolimus and the proliferation signal inhibitors (sirolimus and everolimus) has been shown to be associated with thrombotic microangiopathy. The concomitant presence of strong peritubular capillary staining for C4d on biopsy should raise the suspicion of acute antibody-mediated rejection.

The exact pathogenic mechanism of cyclosporine-induced thrombotic microangiopathy (TMA) remains speculative. Nonetheless, multiple prothrombotic effects of cyclosporine

have been implicated in the pathogenesis of cyclosporine-associated TMA. These include a direct cytotoxic effect on endothelial cells, a reduction of prostacyclin synthesis, and alterations in the thromboxane A2 to prostacyclin ratio, leading to vasoconstriction, platelet aggregation, and thrombus formation.[134] Cyclosporine has also been found to reduce the generation of activated protein C from endothelial cells and to increase thromboplastin expression from mononuclear and endothelial cells. Deficiency in the activity of von Willebrand factor cleaving metalloprotease ADAMTS 13 and the presence of its inhibitory antibodies has been reported to cause TMA in a renal allograft transplant recipient receiving cyclosporine-based immunosuppression. However, whether cyclosporine plays a role in the formation of antibodies to ADAMTS 13 remains to be determined.[135] As is the case with cyclosporine, it is suggested that endothelial cell damage may be the inciting event in tacrolimus-induced TMA. However, tacrolimus has mixed effects on the synthesis of prostaglandins. Subnormal ADAMTS 13 activity level has been suggested to play a contributory role in the development of TMA in a lung transplant recipient receiving tacrolimus-based immunosuppression. No inhibitory antibody was detected. The thrombotic microangiopathic process resolved with plasmapheresis, fresh frozen plasma (FFP), and tacrolimus to cyclosporine conversion therapy. The author concluded that plasmapheresis with FFP as a source of ADMTS 13 and cyclosporine switch may be used as rescue therapy in patients with tacrolimus-induced TMA.[136] However, whether depressed ADAMTS 13 activity level is associated with tacrolimus use remains speculative. Plasma ADAMTS 13 were found to be normal in tacrolimus-treated renal transplant recipients with TMA (Pham PT, unpublished observation). It is likely that the development of CNI-associated TMA is multifactorial.

Sirolimus-induced TMA has been shown to be associated with decreased expression of renal vascular endothelial growth factor (VEGF) and predisposed a subset of patients to the development of TMA.[137] Experimental animal models suggest that VEGF expression is crucial to the preservation and repair of endothelial glomerular and peritubular capillaries,[138] whereas VEGF treatment has been shown to accelerate recovery in an experimental model of TMA.[139] It is speculated that sirolimus-induced alteration of VEGF production is one mechanism by which sirolimus increases the risk of TMA through a "two-hit model." Sartelet and colleagues[137] have suggested that although reduced VEGF levels may occur in all sirolimus-treated patients, only those with concomitant endothelial injury caused by other insults could potentially developed sirolimus-associated TMA. In a small series consisting of five patients, sirolimus-associated TMA was observed in three patients with acute cellular rejection on a calcineurin inhibitor-free regimen: one with chronic graft rejection on a CNI-free protocol and one with chronic CNI nephrotoxicity. However, the possibility that downregulation of VEGF may occur only in patients who have already developed sirolimus-induced TMA cannot be excluded. More recent work in experimental model of TMA have shown that although the proliferation signal inhibitor everolimus inhibits glomerular endothelial cell proliferation and VEGF, no detrimental effects on long-term recovery were demonstrated.[140] Whether alteration of renal VEGF is a predisposing factor for the development of TMA remains to be elucidated.

TMA may develop as early as 4 days postoperative to as late as 6 years posttransplantation. It may be evident clinically by virtue of the typical laboratory findings of intravascular coagulation (e.g., thrombocytopenia, distorted erythrocytes, elevated lactate dehydrogenase levels) accompanied by an arteriolopathy and intravascular thrombi on transplant biopsy. Unlike the primary form of thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome, however, cyclosporine- to tacrolimus-associated TMA may be covert, and the laboratory findings may be inconsistent. In recipients of renal allograft, renal dysfunction is the most common manifestation. Thrombocytopenia and microangiopathic hemolysis are often mild or absent and the diagnsosis is often made on graft biopsies performed to determine the cause of DGF or to rule out acute rejection.[134]

Although there have been no controlled trials comparing the different treatment modalities of this condition, dose reduction or discontinuation of the offending agent appears to be pivotal. Adjunctive plasmapheresis with FFP replacement may offer survival advantages. In transplant recipients with cyclosporine-associated TMA, successful use of tacrolimus immunosuppression has been reported. However, recurrence of TMA in renal transplant recipients treated sequentially with cyclosporine and tacrolimus has been described.[134] In patients with calcineurin inhibitor-associated TMA, successful conversion to sirolimus-based immunosuppression in a CNI-free regimen has been reported.[141] With the increasing use of sirolimus in solid organ transplantation, sirolimus-induced TMA has also been recognized.[142] Indeed, clinicians must remain vigilant for signs and symptoms of recurrence of TMA in patients who are switched from cyclosporine to tacrolimus or vice versa or in those who are switched from a CNI to sirolimus or vice versa. The use of the monoclonal muromonab-CD3 OKT3 has also been associated with the development of posttransplant TMA, although infrequently.

Other potential causative factors of posttransplant-associated TMA include the presence of lupus anticoagulant and/or anticardiolipin antibody, cytomegalovirus infection, and, less frequently, systemic viral infection with parvovirus B19 or influenza A virus.[134] An increased incidence of TMA has been described in a subset of renal allograft recipients with concurrent hepatitis C virus infection and anticardiolipin antibody positivity.[143]

HISTOLOGICAL FEATURES

Cyclosporine and tacrolimus nephrotoxicity have similar appearances in renal allografts. The most common form of acute toxicity is a variant of ATN, with scattered individual necrotic tubular cells, considerable dilatation of tubular lumina and epithelial cell flattening without extensive loss of brush border staining.[144,145] The characteristic feature, often not present, is isometric vacuolization of proximal tubular cell cytoplasm, which tends to involve all tubular cells in few tubular profiles (Figure 37-7).[145] There is mild interstitial edema without significant inflammation or with focal aggregates of inactive lymphocytes often in perivenous locations; tubulitis is absent. There are no specific glomerular abnormalities. Early in the course of toxicity, arterioles have muscular hypertrophy and individual smooth muscle

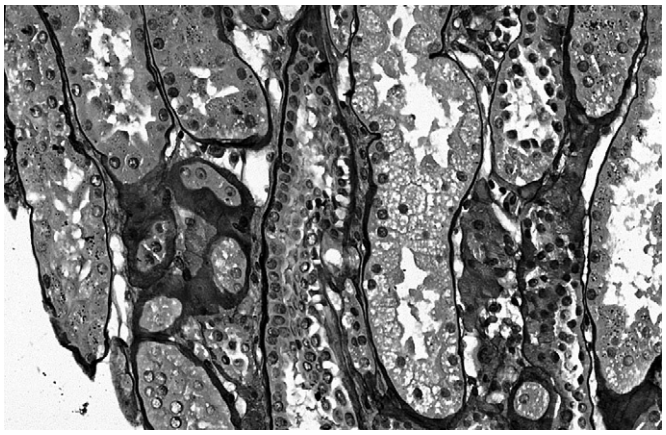


FIGURE 37-7 Acute calcineurin-inhibitor nephrotoxicity. Isometric vacuoles are in the cytoplasm of all epithelial cells in the center proximal tubular profile (Periodic acid methenamine silver × 300).

cells may undergo necrosis; in these locations there is accumulation of rounded plasma protein collections (insudates) in the outer aspect of the muscular walls. The juxtaglomerular apparatus are enlarged.

Calcineurin inhibitors are known to induce thrombotic microangiopathy, which has an identical morphological appearance regardless of the underlying pathogenetic cause. Therefore, the thrombotic microangiopathy associated with the calcineurin inhibitors has the usual features of this entity, including glomerular capillary, arteriolar, and occasionally arterial thrombosis (Figure 37-8).[144,145] Vascular walls display muscular hypertrophy, loose mucoid intimal thickening, and fibrin deposition with luminal narrowing. The thrombotic microangiopathies associated with calcineurin inhibitors have a broad array of renal involvement, ranging from a patchy and subtle process involving only few glomerular capillaries to widespread injury with extensive vascular thrombosis and associated cortical infarction. The thrombotic microangiopathy induced by sirolimus also has an identical appearance within the transplanted kidney. The histological features of chronic cyclosporine and tacrolimus toxicity are discussed in the section on chronic rejection and chronic allograft toxicity.

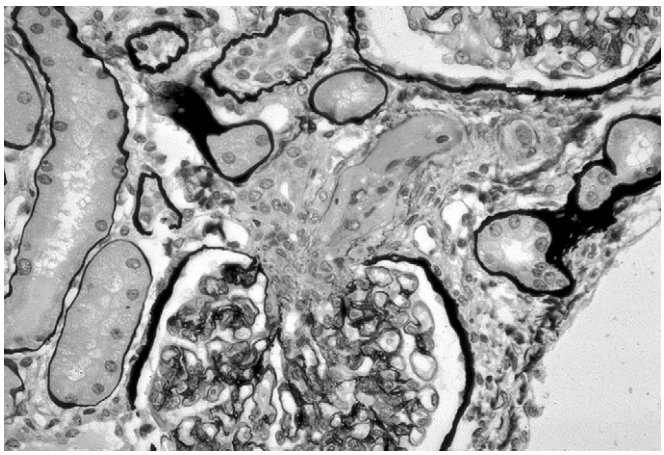


FIGURE 37-8 Thrombotic microangiopathic form of acute calcineurin-inhibitor nephrotoxicity. The glomerulus has bland thrombosis of many capillary lumina with few capillary leukocytes (Masson trichrome × 350).

INFECTION

The most common infections in the early posttransplantation period that are associated with graft dysfunction are urinary tract and CMV infections. Uncomplicated urinary tract infections do not usually lead to graft dysfunction unless they are complicated by pyelonephritis or urosepsis. Clinical CMV infection may mimic acute rejection and is discussed in Chapter 40.

VASCULAR COMPLICATIONS

Renal Artery Stenosis

Transplant renal artery stenosis (RAS) may occur as early as the first week, but it is usually a late complication, occurring 3 months to 2 years posttransplant, with a reported prevalence of 1%-23%.[146] Clinically, patients may present with new onset or accelerated hypertension, acute deterioration of graft function, severe hypotension associated with the use of ACEI, recurrent pulmonary edema or refractory edema in the absence of heavy proteinuria, and/or erythrocytosis. The latter, when associated with hypertension and impaired graft function, should raise the suspicion of RAS (i.e., triad: erythrocytosis, hypertension, elevated serum creatinine). The presence of a bruit over the allograft is neither sensitive nor specific for the diagnosis of graft renovascular disease. However, a change in the intensity of the bruit or the detection of new bruits warrants an evaluation.

Although noninvasive, a radionuclide scan with and without captopril is neither sufficiently sensitive nor specific for detecting transplant RAS (sensitivity and specificity: 75% and 67%, respectively). Color Doppler ultrasound is highly sensitive and serves well as an initial noninvasive assessment of the transplant vessels. It should be noted, however, that color Doppler ultrasound is limited by its relatively low specificity. CO_2 angiography avoids nephrotoxic contrast agents, but its use is not without limitations. Overestimation of the degree of stenosis, bowel gas artifact, and/or patients' intolerance have been reported with the use of CO_2 angiogram.[147] Although gadolinium-enhanced magnetic resonance angiography has been suggested to be an alternative nonnephrotoxic method in identifying transplant renal artery stenosis, its use should be avoided in those with allograft dysfunction due to the association between gadolinium and the development of nephrogenic fibrosing dermopathy (NFD) and systemic fibrosis (NSF). Although invasive, renal nephrogenic angiography remains the gold standard for establishing the diagnosis of RAS.

Graft Thrombosis

Arterial or venous thrombosis generally occurs within the first 2 to 3 postoperative days but may occur as long as 2 months posttransplant. In most series reported, the incidence of graft thrombosis ranges from 0.5% to as high as 8%, with areterial accounting for one-third and venous thrombosis for two-thirds of cases.[45,148] Thrombosis occurring early after transplantation is most often due to technical surgical complications, whereas the later onset is generally

due to acute rejection.[45] In patients with initial good allograft function, thrombosis is generally heralded by the acute onset of oliguria or anuria associated with deterioration of allograft function. Abnormal laboratory findings may include thrombocytopenia, hyperkalemia, and a rising lactate dehydrogenase level. Clinically, the patient may present with graft swelling or tenderness, and/or gross hematuria. In patients with DGF and good residual urine output from the native kidneys, there may be no overt signs or symptoms, and the diagnosis rests on clinical suspicion and prompt imaging studies. The diagnosis is usually made by Doppler ultrasound or isotope flow scan. Confirmed arterial or venous thrombosis typically necessitates allograft nephrectomy. In recipients of kidneys with multiple arteries, thrombosis may occur in a single branch, and depending on the extent of renal parenchymal supplied, adequate functioning tissue may remain.

Suggested predisposing factors for vascular thrombosis include arteriosclerotic involvement of the donor or recipient vessels, intimal injury of graft vessels, kidneys with multiple arteries, history of recurrent thrombosis, thrombocytosis, younger recipient and/or donor age, and the presence of antiphospholipid antibody (anticardiolipin antibody and/or lupus anticoagulant).[146] There has been no consensus on the optimal management of recipients with abnormal hypercoagulability profile, such as abnormal activated protein C resistance ratio or factor V Leiden mutation, antiphospholipid antibody positivity, protein C, or protein S deficiency or antithrombin III deficiency. However, unless contraindicated, perioperative and/or postoperative prophylactic anticoagulation should be considered, particularly in patients with a prior history of recurrent thrombotic events. Transplant of pediatric en bloc kidneys into adult recipient with a history of thrombosis should probably be avoided. The duration of anticoagulation has not been well-defined, but lifelong anticoagulation should be considered in high-risk candidates.[146]

Ureteral Obstruction

Ureteral obstruction occurs in 2% to 10% of renal transplants[149] and often manifests itself as painless impairment of graft function due to the lack of innervation of the engrafted kidney. Hydronephrosis may be minimal or absent in early obstruction, whereas low-grade dilatation of the collecting system secondary to edema at the ureterovesical anastomosis may be seen early posttransplantation and does not necessarily indicate obstruction. A full bladder may also cause mild calyceal dilatation due to ureteral reflux, and repeat ultrasound with an empty bladder should be carried out. Persistent or increasing hydronephrosis on repeat ultrasound examinations is highly suggestive of obstruction. Renal scan with furosemide washout may help support the diagnosis, but it does not provide anatomical details. Confirmation of the obstruction can be made by retrograde pyelogram, but the ureteral orifice may be difficult to catheterize. Although invasive, percutaneous nephrostomy tube placement with antegrade nephrostogram is the most effective way to visualize the collecting system and can be of both diagnostic and therapeutic value.

Blood clots, technically poor reimplant, and ureteral slough are common causes of early acute obstruction after transplantation.[45,150] Ureteral fibrosis secondary to either ischemia or rejection can cause intrinsic obstruction. The distal ureter close to the ureterovesical junction is particularly vulnerable to ischemic damage due to its remote location from the renal artery, thus a compromised blood supply. Although uncommon, ureteral fibrosis associated with polyoma BK virus in the setting of renal transplantation has been well-described.[151] Ureteral kinking, lymphocele, pelvic hematoma or abscess, and malignancy are potential causes of extrinsic obstruction. Calculi are uncommon causes of ureteral obstruction.[45]

Definitive treatmnent of ureteral obstruction due to ureteral strictures consists of either endourological techniques or open surgery. Intrinsic ureteral scars can be treated effectively by endourological techniques in an antegrade or retrograde approach. An indwelling stent may be placed to bypass the ureteral obstruction and be removed cystoscopically after 2 to 6 weeks.[152] An antegrade nephrostogram should be performed to confirm that the urinary tract is unobstructed prior to nephrostomy tube removal. Routine ureteral stent placement at the time of transplantation has been suggested to be associated with a lower incidence of early postoperative obstruction.[153] Extrinsic strictures or strictures that are longer than 2 cm are less likely to be amenable to percutaneous techniques and are more likely to require surgical treatment, as do strictures that fail endourological incision.[152] Obstructing calculi can be managed by endourologic techniques or by extracorporeal shock wave lithotripsy.

Perinephric Fluid Collections

Symptomatic perinephric fluid collections in the early postoperative period can be due to lymphoceles, hematoma, urinoma, or abscesses. Lymphoceles are collections of lymph caused by leakage from severed lymphatics. They typically develop within weeks after transplantation. Most lymphoceles are small and asymptomatic. Generally, the larger the lymphocele, the more likely it is to produce symptoms and require treatment. However, small but strategically positioned lymphoceles may cause unilateral obstruction and necessitate therapeutic intervention. Lymphoceles can also cause compression of the iliac vein leading to ipsilateral leg swelling or deep-vein thrombosis or even to urinary incontinence due to bladder compression.[45]

Lymphoceles are usually detected by ultrasound. They appear as a roundish, sonolucent, septated mass[78] that may be distinguished from other types of perinephric fluid collections such as hematoma or urine leak. Hydronephrosis may be present with or without a visible compressed adjacent ureter. Needle aspiration reveals a clear fluid with a creatinine concentration equal to that of the serum.

No therapy is necessary for the common, small, asymptomatic lymphocele. Percutaneous aspiration should be performed if a ureteral leak, obstruction, or infection is suspected. The most common indication for treatment is ureteral obstruction. If the cause of the obstruction is simple compression resulting from a mass effect of the lymphocele, percutaneous drainage alone usually resolves the problem. Repeated percutaneous aspirations in resistant cases are not

advised because they seldom lead to eventual dissolution of the lymphocele and often result in infection. Lymphoceles can also be marsupialized into the peritoneal cavity, where the fluid is reabsorbed or intraluminally instilled with sclerosing agents such as povidone-iodine, tetracycline, or fibrin-glue. Infected or obstructing lymphoceles can be drained externally. Not uncommonly, the ureter is narrowed due to its inflammatory response to the adjacent lymphocele wall and require reimplantation.

An obstructed hematoma is best managed by surgical evacuation. Urinoma or evidence of a urine leak should be treated without delay. A small leak can be managed expectantly with insertion of a Foley catheter to reduce intravesical pressure. This maneuver may occasionally reduce or stop the leak altogether. Persistent allograft dysfunction, particularly in a symptomatic patient, often necessitates early surgical exploration and repair. Infected perinephric fluid collections should be treated by external drainage or open surgery in conjunction with systemic antibiotics.

GRAFT DYSFUNCTION DURING LONG-TERM FOLLOW-UP

The causes of graft loss after the first year are listed in Table 37-8. Both immunological and nonimmunological factors have been suggested to play an interactive role in the development of chronic allograft dysfunction. Hence, the term *chronic rejection* has been replaced by the less specific but more accurate term *chronic allograft nephropathy*. Graft loss from recurrent diseases is discussed in Chapter 35.

Chronic Rejection and Chronic Allograft Nephropathy

The term *chronic allograft nephropathy* (CAN) first appeared in the Banff schema in 1991 to replace the often misleading term *chronic rejection*. Although initially succeeding in reversing the misconception that not all late scarring of the graft was due to alloimmune injury, over the years the term *CAN* was misused and regarded as a "specific disease" rather than a generic term to describe nonspecific renal parenchymal scarring.[154] In 2005, an International Panel of Experts consisting of clinicians, pathologists, and researchers met at the 8th Banff Conference on Allograft Pathology in Canada to revisit the term *CAN*.[154] It is recommended that CAN should be eliminated and an appropriate classification of chronic allograft injury be used to facilitate treatment and management (see Table 37-8). Nonetheless, CAN currently remains a widely used term to denote chronic allograft dysfunction that involves both alloantigen-dependent and independent factors.

TABLE 37-8 Suggested Banff 2005 Classification of Chronic Allograft Injury

ALLOIMMUNE CAUSES	NONALLOIMMUNE CAUSES
CHRONIC ALLOGRAFT REJECTION	*SPECIFIC CHRONIC DISEASES*
Chronic active antibody-mediated	Chronic hypertension
Chronic active T-cell mediated	CNI toxicity
	Chronic obstruction
	Bacterial pyelonephritis
	Viral infection
	Recurrent or de novo glomerular or vascular diseases
	Recurrent or de novo diabetic changes

CNI, calcineurin inhibitor toxicity.

Alloantigen-Dependent Factors

Acute rejection episodes, poor HLA matching, prior sensitization, inadequate immunosuppression, and noncompliance have all been implicated in the development of chronic allograft dysfunction. In recent years, there has been accumulating evidence suggesting the role of antibody-mediated immune response in the development of chronic allograft injury (CAI).

Acute Rejection Episodes

Numerous retrospective studies have shown that the most significant predictive factor for the development of CAI and late graft loss is the incidence of acute rejection (AR) episodes.[155–158] In some studies, even a single episode occurring within the first 2 months has a negative predictive effect, although multiple episodes and late episodes are more powerful predictors. A single-center retrospective study consisting of nearly 700 consecutive primary deceased donor renal transplant recipients has shown that compared to patients with no AR episodes (NAR), those with late AR (LAR) versus early AR (EAR) (defined as $>$ or <3 months, respectively) had a relative risk of graft failure of 5.27 versus 3.07, respectively ($p < 0.001$).[159] The 5- and 10-year graft survival rates were NAR 87% and 78%, EAR 63% and 55%, and LAR 54% and 28%, respectively.

Treatment of AR episodes after the first year is often followed by incomplete recovery of graft function and accelerated graft loss. In an analysis of the Scientific Registry of Transplant Recipients consisting of all adult primary renal transplant recipients in the more recent era of kidney transplantation (between 1995 and 2000), Meier-Kriesche and colleagues[160] have shown that despite a significant decrease in overall acute rejection rates during the first 6 months and the first year, and in late rejections during the second year after transplantation, there was a lack of improvement in long-term graft survival. Further analysis indicated that since 1995, there has been a trend toward fewer rejections returning to baseline function after treatment. More importantly, the 6-year graft survival rates among patients with AR episodes whose allograft function returned to less than 75% of their baseline renal function was significantly lower than those whose renal function returned to baseline following treatment (38% vs. 72.7%, respectively).

An analysis of the Collaborative Transplant Study database consisting of over 28,000 deceased donor renal transplants performed between 1995 and 2005 demonstrated that the time point of occurrence and the degree of functional recovery after rejection treatment significantly influence the impact of

AR episodes on long-term graft survival. Compared to patients who did not receive rejection treatment during the first posttransplant year, the hazard ratios for graft survival for patients with rejection during three different time periods after transplantation—namely, 0 to 90 days, 91 to 189 days, and 181 to 365 days, were 1.35, 2.05, and 2.74, respectively ($p < 0.001$ for all three time intervals studied).[161]

In addition to the frequency and timing of occurrence, the severity and histopathological type of rejection have also been shown to be predictive of subsequent development of chronic allograft dysfunction. In this respect, early cell-mediated vascular rejections are more likely than tubulointerstitial rejections to herald chronic allograft dysfunction. However, it should be noted that subclinical rejections have also been suggested to result in the early appearance of chronic allograft pathology and impaired graft function at long-term follow-up. In a prospective study consisting of 961 protocol kidney biopsies (from 119 recipients of simultaneous kidney-pancreas transplant and one recipient of kidney alone transplant) performed regularly from the time of transplantation up to 10 years posttransplant, Nankivell and colleagues[162] have shown that the presence of subclinical rejection increased chronic interstitial fibrosis, tubular atrophy, and CAI scores on subsequent biopsies ($p < 0.05$-0.001). More importantly, subclinical rejection preceded and correlated with the development of CA1 on sequential analysis ($p < 0.001$).

ANTIBODY-MEDIATED IMMUNE RESPONSE: THE ROLE OF ANTI-HUMAN LEUKOCYTE ANTIGEN ANTIBODIES IN CHRONIC ALLOGRAFT INJURY

In a retrospective study consisting of 152 renal allograft biopsies performed for evaluation of chronic injury, 23 of 38 (61%) chronic rejection cases had peritubular staining for C4d, compared to 1 of 46 (2%) controls (the former include allograft biopsies showing either glomerular basement membrane duplication in the absence of de novo or recurrent glomerulonephritis or arterial intimal fibrosis with intimal mononuclear cell infiltration, and the latter include allograft biopsies that showed chronic cyclosporine toxicity or nonspecific interstitial fibrosis, and native kidneys with end-stage renal disease). It was further demonstrated that circulating antidonor HLA antibody was present in the majority of C4d-positive chronic rejection cases, whereas it was absent in C4d-negative chronic rejection cases (antidonor HLA positivity: 88% vs. 0%, respectively, $p < 0.002$).[163]

In a 5 year, longitudinal study of 54 kidney transplant recipients with serial determinations of anti-HLA antibodies, Mao and colleagues[164] demonstrated a strong association between anti-HLA antibodies and subsequent graft failure. Of 15 grafts with donor-specific antibodies, 13 failed (defined as a serum creatinine of 4.0 mg/dl). It is notable that sequential testing for HLA antibodies showed that circulating antibodies appeared before a rise in serum creatinine and subsequent graft failure.

Similar to subclinical cell-mediated rejection, subclinical acute AMR has also been suggested to contribute to the development of chronic allograft injury (CAI). In a retrospective review of 83 patients who received HLA-incompatible renal allografts following desensitization protocols to remove donor-specific antibodies (DSA), Haas and colleagues[165] demonstrated a significantly greater mean increase in CAI score on follow-up biopsies of 10 patients with subclinical AMR (follow-up biopsies: 335 ± 248 days), compared to that of 24 recipients without subclinical AMR over a similar follow-up interval (360 ± 117 days).

Histocompatibility

HLA matching is one of the most important predictors for graft survival of both living and deceased donor renal allografts.[166] Among living donor transplants, the half-life for two-haplotype-matched transplants has been estimated to be 22.7 years compared to 13.1 years for one-haplotype matched transplants, which in turn tend to function longer than zero-haplotype-matched and transplants from living, unrelated donors.[167] The importance of matching is particularly evident for deceased donor transplants: six-antigen-matched or zero-mismatched deceased donor transplants have a 5-year survival rate approaching 80% and a half-life approaching 13 years, compared to about to 50% and 8 years, respectively, for completely mismatched transplants.[168]

With the advent of potent immunosuppressive therapy and a decrease in the incidence of acute rejection in recent years, whether matching donor and recipient HLA antigens is still relevant in deceased donor kidney allocation algorithms has been questioned. In a recent analysis of the Collaborate Transplant Study database, Opelz and colleagues[169] demonstrated that while graft survival rates have improved overall over time, the relative impact of HLA matching on the graft survival rates has remained strong and highly significant. Both the need for posttransplant rejection treatment and the graft survival rates showed statistically highly significant associations with HLA matching regardless of the interval analyzed ($p < 0.001$). Among transplants performed between 1985 and 1994, transplants with no HLA mismatches showed a RR of graft failure of 0.76 (95% CI 0.71-0.8), compared to 0.83 for transplants performed in the 1995-2004 decade. The increased risk of failure associated with six HLA antigen mismatches was 1.23 (CI 1.14-1.32) for those transplanted between 1985 and 1994 and 1.16 (CI 1.05-1.27) for those transplanted in the 1995-2004 decade. Analysis of death-censored graft survival showed similar beneficial effect of HLA matches. Although matching is important, the excellent short-term and long-term results of living, unrelated transplants suggest that the condition of the kidney at the time of transplantation is a critical, nonalloantigen-dependent factor.

Prior Sensitization

It has long been recognized that the presence of high levels of preformed, panel-reactive antibodies (PRA) against HLA antigens before transplantation is associated with an increased incidence of rejection episodes and decreased graft survival. In a Collaborative Transplant Study to examine the influence of PRA on graft survival, Opelz and colleagues[170]

demonstrated significantly higher 10-year graft survival among HLA-identical sibling transplants with 0% PRA compared to with those receiving HLA-identical sibling transplants with 1%-50% PRA, or those with greater than 50% PRA. Ten-year graft survival rates were 72.4% versus 63.3% versus 55.5%, respectively ($p = 0.0006$ for 0% PRA compared to with 1%-50% PRA, and $p < 0.0001$ for 0% compared with > 50% PRA). Because transplants from HLA-identical sibling donors do not provide a target for antibodies to HLA antigens, it is speculated that PRA may serve as an indicator of heightened immunity against non-HLA transplantation antigens. Whether graft loss was due to a direct effect of non-HLA humoral sensitization remains to be studied. Nonetheless, the strong association between PRA reactivity and long-term graft loss in HLA-identical sibling donors suggests that non-HLA immunity may play a more important role in clinical transplantation than previously suggested.

Noncompliance and Suboptimal Immunosuppression

The importance of alloantigen-dependent factors is clearly illustrated by the ongoing necessity to maintain adequate immunosuppression for the life span of the graft. The definition of "adequate immunosuppression," however, remains controversial, and long-term prospective randomized trials comparing immunosuppressive regimens of varying intensity have not been performed. In an observational study consisting of over 25,000 renal transplants performed between 1996 and 2005, Opelz and colleagues[171] have shown that in kidney transplant recipients with no history of rejection and good graft function at 1-year posttransplantation, withdrawal or dose reduction of CsA, tacrolimus, or MMF below certain thresholds (reduction of CsA dose to <150 mg/day, tacrolimus to <2 mg/day, of MMF to ≤1 g/day in patients on CsA or ≤0.5 g/day in patients on tacrolimus) during the second-year posttransplant was associated with a statistically significant reduction in graft survival (hazard ratio between 1.37 and 1.65).

A recent prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early corticosteroid withdrawal (at 7 days posttransplant) to long-term, low-dose corticosteroid therapy (5 mg/d after 6 months posttransplant) demonstrated that early corticosteroid withdrawal is associated with an increase in the incidence of biopsy-confirmed acute rejection ($p = 0.04$). Five-year allograft survival and function were similar between the two treatment groups. Of interest, however, posthoc analysis in patients who underwent "for cause" biopsy demonstrated a 5.8% increase in CAI in the corticosteroid withdrawal group through 5 years (9.9% vs. 4.1%, $p = 0.028$).[172]

Noncompliance is a potent cause of late graft loss. Although occasional long-term, stable patients may do fine with discontinuation of immunosuppression, such practice is fraught with danger and should be discouraged unless there is specific overriding indication such as malignancy. The development of an acute rejection episode in a previously stable patient should prompt suspicion of noncompliance or inadequacy of immunosuppression.

Alloantigen-Independent Factors

Alloantigen-independent factors can be classified as donor-related or recipient-related. The former may include donor age, nephron dose relative to recipient's metabolic demand, and donor premorbid conditions such as hypertension, diabetes, or donor preexisting renal dysfunction. The latter may include recipient age, ethnicity, cause of native kidney disease, hypertension, diabetes, dyslipidemia, calcineurin inhibitor nephrotoxicity, number of transplants, proteinuria, and CMV infection. Over the last decade, polyoma BK nephropathy has emerged as an important cause of allograft nephropathy and graft loss. Selected alloantigen-independent factors are discussed below.

Nephron Dose and Hyperfiltration

The concept of nephron dose is based on the presumption that a suboptimal supply of functioning nephrons transplanted to match the demand of the recipient renders the allograft more susceptible to chronic loss of function.[173] The supply of functioning nephrons may be an absolute feature of the allograft (young or old age, female sex, African American race, all of which are associated with a reduced nephron supply) or a feature of perioperative events, such as prolonged ischemia time and ATN. The excellent short- and long-term allograft outcome of dual transplant of marginal kidneys is presumably due to increased viable nephron mass (see dual kidney transplants). In a rat model of chronic rejection, the transplanted kidney appeared to be protected from progressive damage by the presence of a retained, functioning, recipient native kidney.[174] This finding supports the hypothesis that hyperfiltration in the remaining nephrons makes them susceptible to chronic damage in a manner similar to that proposed to explain the inexorable loss of function of the diseased nephrons of patients with chronic kidney disease. Interestingly, in a single-center retrospective study, baseline glomerular hypertrophy (defined on intraoperative biopsies after vascular reanastomosis) was shown to be an important determinant of late allograft dysfunction.[175] In addition to nephron "dose," perioperative damage to the allograft may also contribute to nonspecific tissue injury, cytokine release, upregulation of cell-surface markers and adhesions molecules, and chemoattraction of neutrophils, with further cycles of injury and repair.[176]

Renal function in the first posttransplant year has been shown to serve as a predictor of renal allograft survival regardless of whether or not patient had prior episodes of acute rejection.[177] For recipients of deceased donor renal allografts who had no clinical evidence of acute rejection within 1 year posttransplantation and who had a serum creatinine of less than 1.5 mg/dl at 1 year and a change in serum creatinine of less than 0.3 mg/dl between 6 months and 1 year posttransplant, the estimated median graft half-life is 17 years compared to 5 to 6 years for those who had no acute rejection episodes within 1 year but who had a serum creatinine at 1 year posttransplant of greater than 1.5 mg/dl and a change in SCr of greater than 0.3 mg/dl between 6 months and 1 year posttransplant.

Donor Age

The association between donor age and the development of chronic allograft dysfunction has been well-described. In a retrospective study consisting of 40,289 primary solitary white adult renal transplants, older donor and recipient age were shown to have an independent, yet equally detrimental effect on renal allograft survival.[178]

Hypertension

Independent investigators have shown that posttransplant hypertension is associated with renal allograft failure independent of acute rejection and baseline renal dysfunction.[179–181] Systemic hypertension may exaggerate and perpetuate the vascular injury associated with allograft nephropathy, which has pathological features in common with hypertensive nephrosclerosis.[182] One mechanism by which hypertension could lead to progressive renal allograft dysfunction is by increasing shear stress in renal vessels. It has been suggested that shear stress could promote atherosclerosis and hypertension by causing an upregulation of endothelin-1, PDGF, and other growth factors within the endothelium and by reducing NO secretion.[183] In rat orthotopic renal transplant models, it has been shown that hypertension increases the expression of growth factors and MHC class II.[184] In essence, hypertension may act in concert with or synergistically with immunological factors to cause progressive graft dysfunction.

Calcineurin Inhibitor Nephrotoxicity

Chronic CNI toxicity generally occurs months after transplantation. It may be characterized by an insidious rise in serum creatinine and varying degrees of hypertension and proteinuria. In a longitudinal assessment of CsA nephrotoxicity by protocol histology, a threshold CsA dose of 5 mg/kg/day has been shown to predict worsening of arteriolar hyalinosis on sequential histology. Pathological changes of chronic CsA nephrotoxicity occurred at a median of 3 years and were nearly universal by 10 years.[185] High tacrolimus target levels have also been suggested to play a contributory role in the development of CAI.[185] In a retrospective study comparing protocol biopsies in recipients treated with higher tacrolimus target levels (transplants performed between January 2000 to June 2002; $n = 245$) to those treated with lower tacrolimus target levels (transplants performed between July 2000 and September 2004; $n = 330$), Cosio and colleagues[186] demonstrated that a modest reduction in target tacrolimus levels (15% reduction) in the early posttransplant period were associated with a higher iothalamate GFR ($p < 0.0001$) and a lower incidence and severity of interstitial fibrosis on 1-year protocol biopsies (67% vs. 45%; $p = 0.003$).

Despite a suggested correlation between CNI dose and the severity of chronic CNI toxicity, dosage reduction does not predictably reverse or halt the progression of established chronic renal dysfunction. Accordingly, studies examining protocol biopsies have not consistently demonstrated a correlation between CNI blood concentration levels and chronic histological changes.[187]

Histopathological Features

The term *chronic allograft nephropathy* previously has been used when it is uncertain which immunological and nonimmunological factors have contributed to chronic morphological changes in a renal transplant, although it also has been used synonymously with chronic transplant rejection.[188,189] At the Banff meeting in 2005, it was recognized that the term *CAN* was being misused as a generic categorization of all causes of chronic allograft dysfunction, impeding accurate diagnosis and treatment of the underlying abnormalities responsible for the chronic transplant injury.[154] Therefore, CAN no longer should be used, and an effort is being made to identify diagnostic features in transplant biopsies allowing the creation of an appropriate classification of CAI. The morphological characteristics of all chronic injury in the renal allograft include tubular atrophy and/or tubular dropout with interstitial fibrosis and variable degrees of associated mononuclear inflammation. There may be glomerular and vascular chronic damage as well. The most common causes of CAI are rejection and calcineurin nephrotoxicity, although nephrosclerosis and other nonimmunological factors also play a role.

As with acute rejection, chronic transplant rejection has cell-mediated and antibody-mediated pathogenetic mechanisms. The typical findings in chronic rejection most likely associated with cell-mediated injury include intimal fibrosis of arteries with entrapped mononuclear leukocytes in the thickened vascular wall, disruption of the internal elastic lamina, and narrowing of the lumens.[190] There is tubular atrophy with interstitial fibrosis, and lymphocytes are in the scarred interstitium and in walls of atrophic tubules. Glomeruli may be normal, ischemic, or may show chronic transplant glomerulopathy, a lesion of uncertain pathogenesis consisting of capillary wall double contours, mesangial widening with mild hypercellularity, mesangiolysis, and leukocytes in capillary lumina; segmental glomerulosclerosis may also be present (Figure 37-9).[191] These glomeruli have variable deposition of IgM, complement, and fibrin focally in capillary walls identified by immunofluorescence. Ultrastructurally, mesangial migration and interposition in

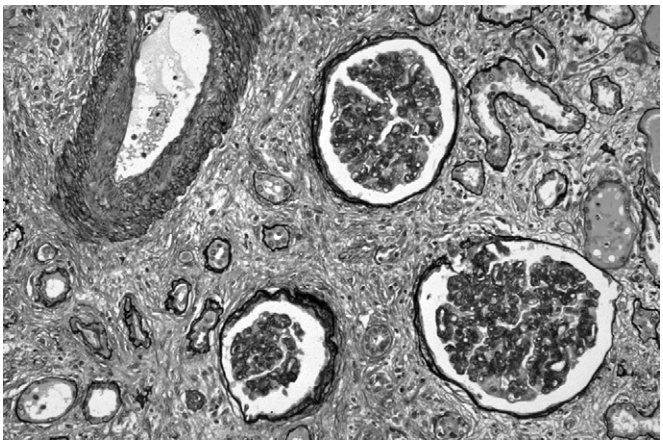


FIGURE 37-9 Chronic rejection. Arterial intimal fibrosis, tubular atrophy with interstitial fibrosis, interstitial lymphocytes, and chronic transplant glomerulopathy are present (Periodic acid methenamine silver × 125).

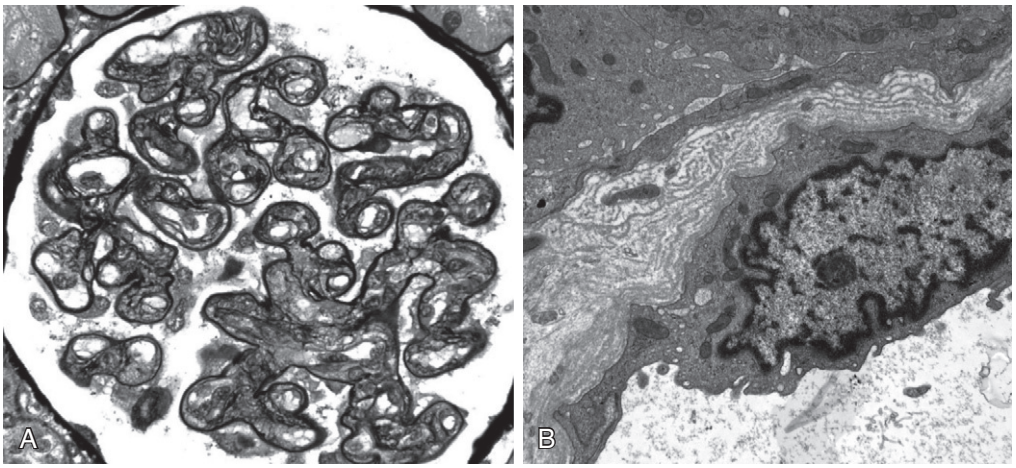


FIGURE 37-10 Biopsy features of chronic antibody-mediated rejection. **A**, Chronic transplant glomerulopathy with reduplicated capillary walls and segmental mesangial expansion (Periodic acid methenamine silver x 350). **B,** Peritubular capillary with multilayered basement membrane and swollen endothelial cell (× 14,000).

capillary walls with subendothelial flocculent material are present. The features reported to be more specifically associated with antibody, mediated chronic rejection include multilayering of glomerular and peritubular capillary basement membranes (Figure 37-10).[192,193] These changes initially occur focally, then become more diffuse as the chronic rejection worsens.[194] Approximately 50% of patients with chronic transplant glomerulopathy will demonstrate concomitant positive C4d staining in peritubular capillaries, indicating a chronic active antibody-mediated rejection process.[195] However, a number of patients with chronic transplant glomerulopathy have no history of DSA or C4d positivity, and complement activation may not be required for the development of this lesion; in these patients it may be a cell-mediated process.[194,196] Interestingly, a number of biopsies demonstrating transplant glomerulopathy lack significant tubulointerstitial scarring, although chronic transplant glomerulopathy confirms that chronic rejection of some type is present. The arterial and glomerular lesions are diagnostic, but tend to be focal and may not be present in a biopsy specimen.

Chronic calcineurin inhibitor toxicity is characterized by focal "striped" interstitial fibrosis, thought to be cortical medullary rays[197] with associated tubular atrophy and little interstitial or tubular inflammation.[198] Arteries are normal, but arterioles may show muscular hypertrophy and rounded insudates in the walls, particularly the outer portion (Figure 37-11). The glomeruli are unremarkable or show mild ischemic change. The chronic toxicity of cyclosporine and tacrolimus cannot be differentiated histologically.[145,198]

As just noted, the CAN no longer is sufficient for diagnosis of chronic allograft morphological changes. The current Banff classification attempts to categorize CAI pathogenetically, classifying it as related to rejection, to another identifiable cause such as calcineurin nephrotoxicity or as of unknown etiology.[154] The Banff '05 meeting report recognizes the possibility of chronic injury alone or with concurrent active rejection. Therefore, chronic active antibody-mediated rejection is now included as a diagnosis in Banff Category 2 (antibody-mediated rejection). Banff Category 4 (T-cell-mediated rejection) includes two chronic diagnoses: chronic active T-cell-mediated rejection and chronic allograft arteriopathy (defined as arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, with formation of neointima). Category 6 includes acute or chronic renal parenchymal damage due to identifiable causes other than rejection, such as chronic infection, calcineurin inhibitor toxicity, obstruction, and so on. Category 5 encompasses all types of chronic injury for which no specific etiology can be determined, has nonspecific language using the terminology interstitial fibrosis and tubular atrophy, no evidence of any specific etiology, and is graded by the severity of the tubulointerstitial scarring.

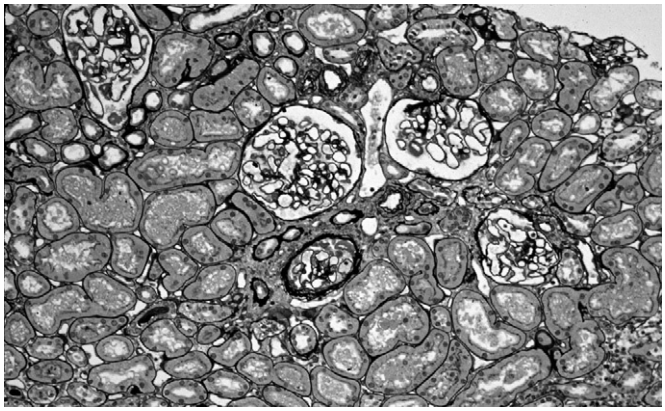


FIGURE 37-11 Chronic calcineurin-inhibitor nephrotoxicity. There is "striped" tubular atrophy with interstitial fibrosis, without a significant lymphocytic infiltrate. The intervening tubules are unremarkable as are the majority of glomeruli. The small glomerulus has mild ischemic features (Jones methenamine silver × 125).

Clinical Course

Chronic rejection typically occurs in patients who have suffered episodes of acute rejection, particularly when these episodes are multiple or late or when recovery of graft function, as judged by the return of the serum creatinine level to

baseline, is incomplete. It presents clinically as deterioration of graft function, typically with proteinuria of varying degrees and hypertension. The time course to allograft failure is extremely variable, ranging from months to years. In most cases, the loss of graft function is inexorable, although spontaneous reduction and arrest of the rate of decline may occur. Chronic rejection is the most common cause of transplant nephrotic syndrome.

Renal function in chronic rejection is typically monitored by the rise of the serum creatinine. Creatinine clearance, however, may overestimate the true GFR in the presence of chronic allograft dysfunction and proteinuria. As a result, the early stages of graft dysfunction may be associated with apparently minor rises in the SCr level, whereas small changes in GFR produce big changes in creatinine levels as the graft approaches end-stage failure.

Differential Diagnosis

Chronic rejection needs to be differentiated from other causes of late graft dysfunction. The absence of a history of rejection, hypertension, and proteinuria should raise diagnostic skepticism. A renal ultrasound with Doppler should be performed at least once to exclude obstructive causes of graft dysfunction and the possibility of RAS particularly in the setting of new or worsened hypertension and/or erythrocytosis. Kidney biopsy provides a definitive diagnosis and a good estimate of the severity of the lesion.

Treatment

The optimal management of immunosuppression for the chronically failing allograft has yet to be defined. If an element of acute rejection is suspected, a steroid pulse may be given, but the therapy should not be repeated if clinical improvement does not occur. Monoclonal and polyclonal antibodies should not be given for chronic rejection. Intensification of CNI therapy often merely exaggerates nephrotoxicity. In contrast, a reduction or cessation of CNI in conjunction with the addition, continuation, or increase in the dose of mycophenolate MMF may slow the rate of decline of renal function in patients with biopsy-proven CAI and deteriorating allograft function.

Recent 15-year outcome data from a single-center randomized controlled trial comparing continued CsA therapy (n = 114) with azathioprine conversion therapy (n = 102) 1 year after transplantation in stable renal transplant recipients defined as SCr < 3.9 mg/dl 300 μgmol/L with no acute rejection within the preceeding 6 months demonstrated significantly better renal function in those randomized to azathioprine conversion therapy at 10-year follow-up. However, this effect was lost at 15 years posttransplant. There was no statistically significant difference in patient and graft survival and death-censored graft survival between the two treatment groups.[199] Whether azathioprine conversion therapy in patients with established CAI offers graft survival advantage over CsA-based immunosuppression is unknown.

Conversion from cyclosporine or tacrolimus to sirolimus is yet another suggested strategy to preserve graft function in patients with biopsy-confirmed CAI. A metaanalysis of 5 randomized (n = 1040 patients) and 25 nonrandomized (n = 977 patients) trials comparing renal function in patients undergoing CNI to sirolimus conversion therapy for chronic allograft dysfunction demonstrated a beneficial effect of sirolimus conversion therapy on short-term renal function.[200] However, sirolimus was discontinued in 28% of patients in the randomized trials and 17% in the nonrandomized trials. Given the high discontinuation rate, large randomized trials with longer follow-up are needed to determine whether sirolimus conversion therapy leads to an overall favorable outcome. Of note, sirolimus use has been reported to be associated with dyslipidemia and proteinuria. Whether the development of proteinuria specifically associated with sirolimus adversely affects cardiovascular disease risk is currently unknown and awaits studies. Posttransplant proteinuria in general has been shown to be an independent risk factor for graft loss and cardiovascular disease and related death.[201] Anecdotal reports in small series of patients suggested a beneficial effect of azathioprine or MMF to leflunomide conversion therapy in stabilizing or reversing the progression of chronic allograft dysfunction during short-term follow-up.[202]

Although CNI dose reduction or withdrawal in conjunction with MMF or sirolimus treatment may improve or slow the progression of CAI, manipulation of immunosuppressive therapy may be of little beneficial effect when SCr is 3 to 3.5 mg/dl or higher (unpublished observation), particularly when there is evidence of significant proteinuria at the time of therapeutic intervention or when there is evidence of significant chronic histological changes on biopsy. In a study of 59 renal transplant patients undergoing sirolimus conversion therapy for deteriorating graft function and histological signs of CNI toxicity, baseline proteinuria of greater than 800 mg/day compared with baseline proteinuria of less than 800 mg/day was found to be associated with a relative risk of graft loss of 3.98 ($p < 0.001$) during a follow-up period of up to 5 years.[203]

The relative contribution of nonimmmunological mechanism(s) to the development of progressive allograft dysfunction is difficult to define, and the management of CAI should be targeted at risk factor modification. Blood pressure control and aggressive management of dyslipidemia and proteinuria are mandatory. Target low-density lipoprotein (LDL) concentrations should be maintained at less than 100 mg/dl (optional <70 mg/dl).

In the nontransplant settings, the use of ACEI and/or ARB has been shown to reduce proteinuria and slow the progression of chronic kidney disease. The beneficial effects of ACEI or ARB on posttransplant patients and graft survival have not been consistently demonstrated.[204,205] In a metaanalysis of 21 randomized controlled trials (n = 1549 patients) conducted to determine the effect of ACE-inhibitor or ARB use following kidney transplantation with a median follow-up of 27 months, ACEI and ARB use was associated with clinically important reductions in proteinuria (−0.47 gm/d; 95% CI −0.86 to −0.08), hematocrit (−3.5%; 95% CI −6.1 to −0.95), and GFR (−5.8 mL/min; 95% CI −10.6 to −0.99). However, there were insufficient data to determine the effect of ACEI or ARB use on patient or graft survival.[206] Of interest, results of a small single-center double-blind, placebo-controlled, crossover study demonstrated that compared to placebo and β-blocker

(carvedilol), the use of ARB (losartan) for a period of 8 weeks reduces urine excretion of proteins associated with tubular damage and graft fibrosis—namely, transforming growth factor beta-1 (TGF-beta1) and amino-terminal propeptide of type III procollagen (PIIINP).[207] Further recommendations on the routine use of ACEI and/or ARB await large, randomized controlled clinical trials with long-term follow-up. Nonetheless, ACEI and/or ARB are commonly used due to its well-established antiproteinuric and cardioprotective effect. These drugs should be used with care because of their potential to cause or exacerbate anemia, hyperkalemia, and renal dysfunction. A rising serum creatinine should alert clinicians to the possibility of RAS.

In addition to pharmacological treatment, emphasis should be placed on lifestyle modifications, including moderation of dietary sodium and saturated fat intake, regular aerobic exercise, weight reduction, and tobacco avoidance. Similar to chronic kidney disease in the nontransplant settings, the management of CAI requires a multidisciplinary approach where every potentially complicating factor must be closely monitored and treated.

BK Nephropathy

Over the last decade, BK virus associated nephropathy has emerged as an important cause of allograft dysfunction following renal transplantation. BK nephropathy (BKN) most commonly presents with an asymptomatic rise in serum creatinine between 2 to 60 months after engraftment (median 9 months).[208] It has been reported to occur as early as the first week to as late as 6 years posttransplant. The diagnosis of BKN is made by allograft biopsy, which demonstrates BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium.[209,210] There are variable degrees of interstitial mononuclear inflammation often with many plasma cells, degenerative changes in tubules, and focal tubulitis that can mimic acute rejection (Figure 37-12). BKN often is associated with very focal and sharply demarcated areas of tubulointerstitial inflammation, corresponding to foci of viral infection. Additional studies including immunohistochemistry, in situ hybridization, or electron microscopy are required to confirm the diagnosis. Approximately 50% of biopsies showing BKN also will have tubular basement membrane deposition of immune complexes, which contain BK viral antigens.[211] BK infection and acute rejection may occur simultaneously, and distinguishing between BKN, acute rejection, or the concomitant presence of both processes can be a diagnostic challenge. In the late stage of BKN, few characteristic intranuclear inclusions are seen, and the histopathological changes may be indistinguishable from those of chronic rejection or nonspecific interstitial fibrosis and scarring but usually with marked inflammation. There is a histological classification system for BKN based on the degree of active inflammation, acute tubular injury, and tubulointerstitial scarring, which may have prognostic significance.[212] Urine cytology for decoy cells[213] or quantitative determinations of viuria and of viral load in blood have been proposed as surrogate markers for the diagnosis of BKN.

There is no standard protocol for the treatment of BKN. Nonetheless, immunological containment of BK virus replication should be the mainstay of therapy. Suggested strategies for reduction in immunosuppression include reduction or discontinuation of antimetabolites (mycophenolate or azathioprine) with judicious reduction in calcineurin inhibitor therapy or other immunosuppressive regimen. Switching from tacrolimus to cyclosporine or to sirolimus has resulted in resolution of BKN and viremia/viuria in anecdotal case reports.[208] CNI to sirolimus switch has been suggested to have the added benefit of avoiding the long-term nephrotoxic effect of CNI therapy. Although no approved antiviral drug is available, reduction in immunosuppression and adjunctive therapy with leflunomide, cidofovir, quinolones, or intravenous immunoglobulin (IVIG)[214] have been used with variable success and should be considered in patients with progressive allograft dysfunction. The choice of antiviral agents varies among centers. Quinolones are preferred by some centers due to its low cost and ease of administration, whereas leflunomide is used by others due to its

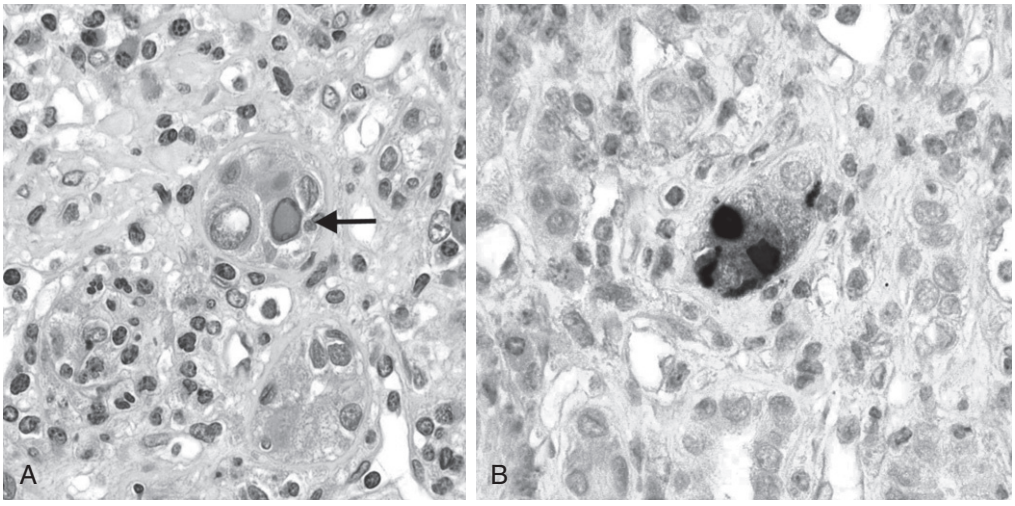


FIGURE 37-12 Polyoma virus (BK) nephropathy. **A,** Enlarged tubular epithelial cells with an intranuclear viral inclusion *(arrow)* and mononuclear inflammation in the tubules and interstitium (Hematoxylin and eosin × 350). **B,** Immunohistochemical stain for polyoma virus (SV40) demonstrating an intranuclear viral antigen in a tubule (× 350).

potential simultaneous antiviral and immunosuppressive properties. Leflunomide has been reported to prevent acute rejection and delay progression of chronic allograft injury (CAI) in animal models. Limited studies in renal transplant recipients have also demonstrated a beneficial effect of leflunomide in reversing the progression of chronic allograft dysfunction with minimal toxicity.[202] The use of cidofovir is limited by its nephrotoxicity, particularly at the doses used for the treatment of systemic cytomegalovirus infection (5 mg/kg weekly). However, cidofovir is highly concentrated in urine and renal tissue, and the use of low-dose cidofovir in BKN has been reported to be devoid of nephrotoxicity or serious adverse events. In a series of 21 patients with BKN with irreversible deterioration of graft function, renal function stabilized in cidofovir-treated patients and no graft loss occurred during 24.8 (8-41) months follow-up (n = 8). No cidofovir-related renal toxicity occurred. In contrast, 9 of 13 patients who received no adjuvant cidofovir therapy lost their graft after a median of 8 (4-40) months.[215] Anecdotal reports suggested that IVIG may be effective in treating steroid-resistant rejection,[216,217] and its use may be beneficial in patients with concomitant rejection and BKN or in those with histopathological changes that are indistinguishable from those of rejection.

Despite various treatment strategies, up to 30% to 50% of patients with established BKN developed progressive decline in renal function with graft loss. Early diagnosis and intervention may improve prognosis. Intensive monitoring of urine and serum for BK by PCR during the first year post-transplantation and preemptive reduction of immunosuppressive therapy are associated with resolution of viremia and absence of BK nephropathy without acute rejection or graft loss.[218]

A full list of references are available at www.expertconsult.com.

Chapter 38

INFECTION IN RENAL TRANSPLANT RECIPIENTS

Camille Nelson Kotton, M.D., and Emilio Ramos, M.D.

The prevention and treatment of infection is central to the optimal management of transplant recipients. Successful avoidance and management of infections in the immunocompromised renal transplant recipient are complicated by a variety of factors.[1] These include increased susceptibility to a broad spectrum of infectious pathogens, difficulty in making a diagnosis of infection in the face of diminished signs and symptoms of infection, an array of noninfectious etiologies of fever (e.g., graft rejection, drug toxicity), and the possibility that multiple processes are present simultaneously. Further, because immunocompromised patients tolerate invasive and established infection poorly with high morbidity and mortality, the urgency for an early and specific diagnosis to guide antimicrobial therapy is increased. Given the primacy of T lymphocyte dysfunction in transplantation, viral infections in particular are increased and contribute to systemic illness, graft dysfunction and rejection, and enhance the risk for other opportunistic infections (e.g., *Pneumocystis* and *Aspergillus* species) and for virally-mediated cancers.

RISK OF INFECTION

The risk of infection in the renal transplant recipient is determined by the interface of two factors:

1. The epidemiological exposures of the organ recipient and the donor, including those unrecognized by the patient or distant in time (Table 38-1); exposures of importance include environmental, community, and nosocomial-acquired exposures.
2. The patient's net state of immunosuppression, including all of the factors contributing to the risk for infection in the transplant recipient (Table 38-2)

Epidemiological Exposures

Further evaluation of the epidemiology of the patient allows the clinician to establish a differential diagnosis for a given "infectious" presentation and to design the optimal preventive strategy for each patient. Donor and recipient screening prior to transplantation are critical components to the post-transplantation health maintenance of the patient (Table 38-3). Empiric therapy or prophylaxis should be strongly considered in transplant recipients with latent infection with tuberculosis (TB), *Strongyloides stercoralis*, coccidiomycosis, and for patients known to have received organs from donors with acute bacterial and fungal infections. Specific antiviral strategies stratified according to individual risk should be considered for all kidney recipients.

Donor-Derived Infections

Infections transmitted from the donor tissue(s) to the recipient are among the most important exposures in transplantation, as the recipient is likely to be nonimmune and

TABLE 38-1 Significant Epidemiological Exposures Relevant to Transplantation

DONOR-DERIVED
Viral
Herpes family (cytomegalovirus, Epstein-Barr virus, human herpes viruses 6, 7, 8, herpes simplex)
Hepatitis viruses (notably B and C, newly emerging E)
Retroviruses (HIV, HTLV-1 and -2)
Others (LCMV, rabies)
Bacteria
Gram-positive and gram-negative bacteria (*Staphylococcus* species, *Pseudomonas* spp., Enterobacteriaceae)
Mycobacteria (tuberculosis and nontuberculous)
Nocardia asteroides
Fungi
Candida species
Aspergillus species
Endemic fungi (*Cryptococcus neoformans*)
Geographic fungi (*Histoplasma capsulatum, Coccidioides immitis, Blastomyces*)
Parasites
Toxoplasma gondii
Trypanosoma cruzi
NOSOCOMIO EXPOSURE
MRSA
VRE; linezolid and quinupristin-dalfopristin resistance also reported
Aspergillus species
Candida nonalbicans strains
COMMUNITY EXPOSURE
Food and water-borne (*Listeria monocytogenes*, *Salmonella* spp., *Cryptosporidium*, hepatitis A, *Campylobacter* spp.)
Respiratory viruses (RSV, influenza, parainfluenza, adenovirus, metapneumovirus)
Common viruses: often with exposure to children (Coxsackie, parvovirus B19, rotavirus, polyomavirus, papilloma virus)
Atypical respiratory pathogens (*Legionella* spp., *Mycoplasma* spp., *Chlamydia*)
Geographic fungi, *Cryptococcus*, *Pneumocystis jiroveci*
Parasites (often distant)
Strongyloides stercoralis
Toxoplasma gondii
Leishmania species
Trypanosoma cruzi (Chagas disease)
Naegleria spp. (Acanthamoeba)

HIV, human immuodeficiency virus; *HTLV*, human T lymphotroic virus; *LCMV*, lymphocytic choriomeningitis virus; *MRSA*, methicillin-resistant staphylococci; *RSV*, respiratory syncytial virus; *VRE*, vancomycin-resistant enterococci.

TABLE 38-2 Factors Contributing to the Net State of Immunosuppression

Immunosuppressive therapy: type, intensity, duration
Prior therapies (chemotherapy or antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Neutropenia, lymphopenia (often drug-induced)
Underlying immune deficiency
Hypogammaglobulinemia from immunosuppression, proteinuria or malnutrition
Systemic lupus, complement deficiencies
Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis
Viral infection (CMV, hepatitis B and C, HIV, RSV, EBV)
Graft rejection
Cancer/cellular proliferation

CMV, cytomegalovirus; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *RSV*, respiratory syncytial virus.

significantly immunosuppressed. Some of these infections are latent, while others are the result of bad timing, with active infection transmitted at the time of transplantation. Numerous such infections have been recognized in transplant recipients, ranging from common and expected pathogens to unexpected pathogens such as lymphocytic choriomeningitis virus,[1] Chagas disease,[2] rabies,[3] and TB. Three types of infection merit special attention. First, in donors who are bacteremic or have fungemia at the time of donation, such infections (staphylococci, pneumococcus, *Candida* species, *Salmonella, Escherichia coli*) may tend to "stick" to anastomotic sites (vascular, urinary) and may produce leaks, mycotic aneurysms, or surgical site infections. Second, viral infections, including cytomegalovirus (CMV) and Epstein-Barr virus (EBV), are associated with particular syndromes and morbidity in the immunocompromised population (discussed later in text); the greatest risk of such infections is in recipients who are seronegative (immunologically naïve) and receive infected grafts from seropositive donors (with latent or active viral infection). Third, latent infections, including TB, may activate many years after the initial exposure. Disseminated mycobacterial infection is often difficult to treat once established largely because of the significant immunosuppression and interactions between the antimicrobial agents used to treat infection (e.g., rifampin, streptomycin, isoniazid) and the agents used in immune suppressive therapy.

Given the risk of transmission of infection from the organ donor to the recipient, certain infections should be considered relative contraindications to organ donation. Given that renal transplantation is, in general, elective surgery, it is reasonable to avoid donation from individuals with unexplained fever, rash, or infectious syndromes. Some of the common criteria for exclusion of organ donors are listed in Table 38-4; the U.S. Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Definition of Eligible Death, Policy 7.1.8 may also provide further guidance.

Recipient-Derived Exposures

Infections in recipient-derived exposures are generally latent infections activated in the setting of immune suppression. It is necessary to obtain a careful history of travel and exposures to guide preventive strategies and empiric therapies. Notable among these infections are TB, strongyloidiasis, viral infections (herpes simplex virus [HSV] and varicella zoster or shingles), histoplasmosis, coccidioidomycosis, hepatitis B or C, and human immunodeficiency virus (HIV). Vaccination status should be evaluated (tetanus, hepatitis B, varicella and varicella zoster, childhood vaccines, influenza, pneumococcal vaccine). Dietary habits should also be considered,

TABLE 38-3 The Pretransplantation Evaluation of the Donor and Recipient (Consider the Following)

LABORATORY TEST	ALL PATIENTS	PATIENTS WITH EXPOSURE TO ENDEMIC AREA	QUANTITATIVE VIRAL STUDIES AVAILABLE (PCR)
Serologies			
CMV	√		√
HSV	√		√
VZV	√		
EBV	√		√
HIV	√		√
HBV: HbsAg	√		√
anti-HBs	√		
HCV	√		√
Treponema pallidum	√		
Toxoplasma gondii	√		
Strongyloides stercoralis		√	Stool ova and parasite
Leishmania spp.		√	Biopsy of affected region
Trypanosoma cruzi		√	Blood smear
Histoplasma capsulatum		√	Body fluid antigen assay
Cryptococcus neoformans		√	Cryptococcal antigen
Coccidioides immitis		√	Body fluid antigen assay
Cultures, etc.			
Urinalysis and culture	√		
Skin test: PPD or QuantiFERON Gold		√	
Chest x-ray (routine)	√		
Stool ova and parasites		√	
Urine ova and parasites/cystoscopy			√ (for kidneys, in *Schistosoma* endemic areas)

CMV, cytomegalovirus; *EBV*, Epstein-Barr virus; *HBV*: HbsAg, hepatitis B surface antigen; *HCV*, hepatitis C virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *PPD*, purified protein derivative (tuberculin); *VZV*, varicella zoster virus.

including the use of well water (*Cryptosporidia*), uncooked meats (*Salmonella, E. coli, Campylobacter*), and unpasteurized dairy products and luncheon meats (*Listeria*).

Community Exposures

Common exposures in the community are often related to ingestion of contaminated food and water, exposure to infected children or coworkers, or exposures due to hobbies (gardening), travel, or occupation. Respiratory virus infections due to influenza, respiratory syncytial virus, and adenoviruses increase the risk for both viral pneumonia and subsequent bacterial superinfection. Community (and solid-organ or transfusion-associated) exposures to CMV and EBV may produce severe primary infection in the nonimmune host. Recent and remote exposures to endemic, geographically restricted systemic mycoses (*Blastomyces dermatitidis, Coccidioides immitis,* and *Histoplasma capsulatum)* and *Mycobacterium tuberculosis* can result in localized pulmonary, extrapulmonary, or disseminated infections. Asymptomatic *S. stercoralis* infections may reactivate decades after initial exposure in the setting of immunosuppressive therapy. Such reactivation can result in either a gastrointestinal illness with parasite migration and hyperinfestation syndrome (characterized by hemorrhagic enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying (usually) gram-negative bacteremia or meningitis. Gastroenteritis due to *Salmonella* species, *Campylobacter jejuni*, and a variety of enteric viruses can result in more

TABLE 38-4 Common Infectious Exclusion Criteria for Organ Donors*

Active, uncontrolled or undiagnosed infectious diseases
Unknown infection of central nervous system (encephalitis, meningitis)
Herpes simplex encephalitis or other encephalitis
JC virus infection
West Nile virus infection
Rabies
CJD or variant CJD
Other fungal or viral encephalitis
Cryptococcal infection of any site
Untreated bacterial meningitis (proof of cure)
Infection with HIV (serological or molecular)
Active viremia: herpes, acute EBV (mononucleosis)
Serological or molecular evidence of HTLV-I/II*
Active hepatitis A, B, C*
Active infection with *Leishmania*, *Strongyloides*, *Toxoplasmosis*, or malaria
Latent or active *Trypanosoma cruzi* (Chagas disease) infection
Active tuberculosis
SARS
Untreated pneumonia
Untreated bacterial or fungal sepsis (e.g., candidemia)
Untreated syphilis
Multisystem organ failure due to overwhelming sepsis, gangrenous bowel

*Must be considered in the context of the individual donor and recipient.
CJD, Creutzfeldt-Jacob disease; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *HTLV*, human T lymphotroic virus; *SARS*, severe acute respiratory syndrome.

severe and prolonged diarrheal disease with persistent infection and an increased risk of translocation into the bloodstream and metastatic infection.

Nosocomial Exposures

Nosocomial infections are of increasing importance because organisms with significant antimicrobial resistance predominate in many centers. These include vancomycin, linezolid and quinupristin/dalfopristin-resistant enterococci, methicillin-resistant staphylococci (MRSA), and fluconazole-resistant *Candida* species. Excessive antimicrobial use has resulted in increased rates of *Clostridium difficile* colitis. Outbreaks due to *Legionella* species have been associated with hospital plumbing and contaminated water supplies or ventilation systems. Nosocomial spread of *Pneumocystis jiroveci* between immunocompromised patients has also been suggested by a variety of case series. Respiratory viral infections may be acquired from medical staff and should be considered among the causes of fever and respiratory illness among hospitalized or institutionalized, immunocompromised individuals. Influenza vaccination of staff members may decrease transmission to immunocompromised hosts. Each nosocomial infection should be investigated to ascertain the source and prevent subsequent infections.

Net State of Immunosuppression

The net state of immunosuppression is a measure of all of the factors contributing to the patient's risk for infection (see Table 38-2). Among these are:

1. The specific immunosuppressive therapy, including dose, duration, and sequence of agents
2. Technical problems from the transplant procedure, resulting in leaks (blood, lymph, urine) and fluid collections, devitalized tissue, poor wound healing, and the use of surgical drainage catheters for prolonged periods
3. Prolonged airway intubation
4. Prolonged use of broad-spectrum antibiotics
5. Renal and/or hepatic dysfunction
6. Prolonged use of vascular access or dialysis catheters
7. Presence of infection with one of the immunomodulating viruses, including CMV, EBV, hepatitis B (HBV) or C (HCV), or HIV.

Specific immunosuppressive agents are associated with increased risk for certain infections (Table 38-5). Combinations of these agents may enhance this risk or cause toxicity (e.g., nephrotoxicity) and may further enhance risk.

TABLE 38-5 Specific Immunosuppressive Drugs and Infection

Antilymphocyte globulins (lytic) and alloimmune response: Activation of latent (herpes) virus, fever, cytokine release
Plasmapheresis: Encapsulated bacteria, activation of latent CMV
Costimulatory blockade: Altered memory T-cell responses
Corticosteroids: Bacteria, PCP, hepatitis B, C
Azathioprine: Neutropenia, papilloma virus?
MMF: Early bacterial infection, B-cells, late CMV
Calcineurin inhibitors (cyclosporine/tacrolimus): Enhanced viral replication (absence of immunity), gingival infection, intracellular pathogens
Sirolimus: Excess infections in combination with current agents

CMV, cytomegalovirus; *MMF*, mycophenolate mofetil; *PCP*, *Pneumocystis jiroveci* pneumonia.

TIMETABLE OF INFECTION

As immunosuppressive regimens have become more standardized, the most common infections that tend to occur in a somewhat predictable pattern depending on the time elapsed since transplantation (Figure 38-1). This is a reflection of the changing risk factors that influence infection, including surgery and hospitalization, immune suppression, acute and chronic rejection, emergence of latent infections, and exposures to novel community infections.[4] The pattern of infections will be changed with alterations in the immunosuppressive regimen (pulse dose steroids or intensification for graft rejection), intercurrent viral infection, neutropenia (drug toxicity), graft dysfunction, or significant epidemiological exposures (travel or food).

The timeline reflects the following three overlapping periods of risk for infection: 1) the perioperative period to approximately 4 weeks after transplantation, 2) the period 1 to 6 months after transplantation (depending on the rapidity of taper of immune suppression and the type and dosing of antilymphocyte "induction" that may persist), and 3) the period beyond the first year after transplantation. These periods reflect the evolving major risk factors associated with infection, with surgery and technical complications, followed by the intensive immune suppression with viral activation, and subsequently the community-acquired exposures with the return of normal activities.

The timeline may be used in a variety of ways: to establish a differential diagnosis for the transplantation patient suspected of having infection; as a clue to the presence of an excessive environmental hazard for the individual, either within the hospital or in the community; and as a guide to the design of preventive antimicrobial strategies. Infections occurring outside the usual period or of unusual severity may suggest either excessive epidemiological hazard or excessive immunosuppression. The prevention of infection must be linked to the risk for infection at various times after transplantation. Routine preventive strategies from the Massachusetts General Hospital, Boston, are outlined in Table 38-6. It should be noted that such strategies serve only to delay the onset of infection in the face of epidemiological pressure. The use of antibiotic prophylaxis, vaccines, and behavioral modifications (e.g., routine handwashing or advice against digging in gardens without masks) may only result in a shift to the right of the infection timeline, unless the intensity of immune suppression is reduced or immunity develops.

Phase One: 1 to 4 Weeks after Transplantation

During the first month after transplantation, three types of infection occur. The first type of infection was present in the recipient prior to transplantation; it was either unrecognized or inadequately treated, and now has emerged in the setting of surgery, anesthesia, and immunosuppression.

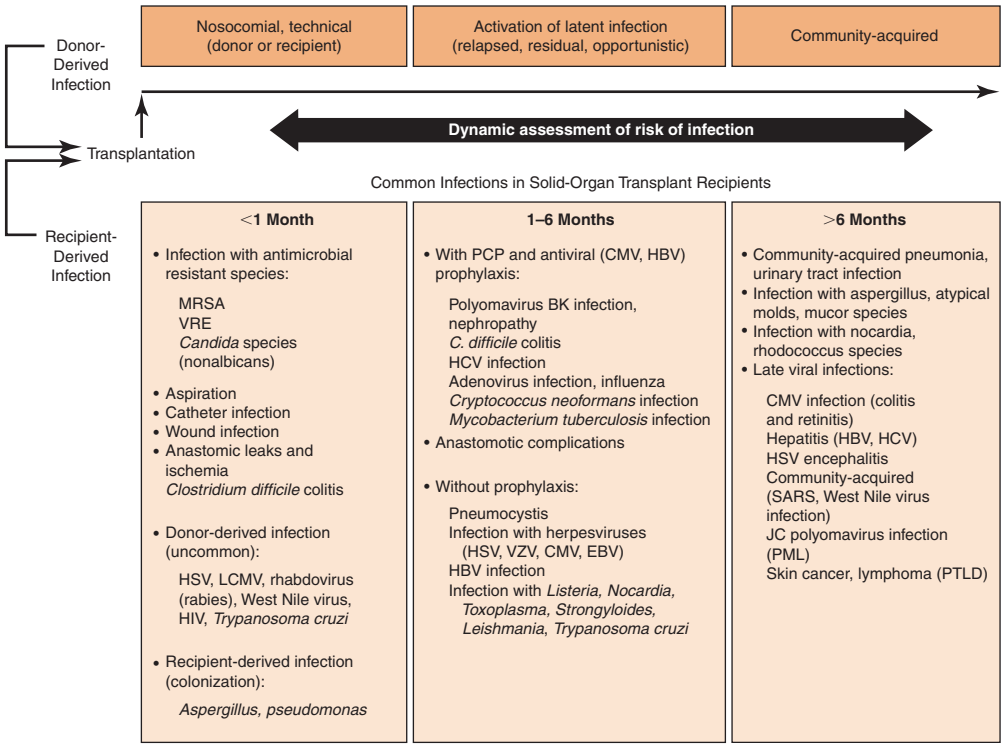


FIGURE 38-1 The timeline of posttransplantation infections. (Adapted from J.A. Fishman, Infection in solid-organ transplant recipients, N.Engl .J. Med. 357 [25] [2007] 2601–2614.) *HBV*, hepatitis B virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *LCMV*, lymphocytic choriomeningitis virus; *MRSA*, methicillin-resistant *staphylococcus aureus*; *PCP*, *Pneumocystis jiroveci* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *PTLD*, post-transplantation lymphoproliferative disorder; *SARS*, severe acute respiratory syndrome; *VRE*, vancomycin-resistant *Enterococcus faecalis;*; and *VZV*, varicella-zoster virus.

Pretransplantation pneumonia and vascular access infections are common examples of this type of infection. Colonization of the recipient with resistant organisms is also common (e.g., MRSA). The first rule of successful transplant infectious disease control is the eradication of all active infection prior to transplantation.

The second type of early infection was present in the donor before transplantation. This is often a nosocomial-acquired organism (resistant gram-negative bacilli and *Staphylococcus aureus* or *Candida* species) due to either systemic infection in the donor (e.g., line infection) or contamination during organ procurement. The result is a high risk of infection of vascular suture lines with resultant mycotic aneurysm. Uncommonly, infections have been transmitted from donor to recipient, including TB or fungal infections (e.g., histoplasmosis) that emerge earlier in the timeline than expected (i.e., in the first month).

The third type and the most common source of infections in this early period is related to the complex surgical procedure of transplantation. These include surgical wound infections, pneumonia (aspiration), bacteremia due to vascular access or surgical drainage catheters, urinary tract infections, or infections of fluid collections (due to leaks of vascular or urinary anastomoses or lymphoceles). These are nosocomial infections and, as such, are due to the same bacteria and *Candida* infections observed in nonimmunosuppressed patients undergoing comparable surgery but with the immune suppression, the signs of infection may be subtle and the severity or duration may be greater. The technical skill of the surgeons and meticulous postoperative care (i.e., wound care, endotracheal tubes, vascular access devices, and drainage catheters) are the determinants of risk for these infections. Also among the common infections is *C. difficile* colitis. Limited perioperative antibiotic prophylaxis for renal transplantation (i.e., from a single dose to 24 hours of an antibiotic such as cefazolin) is usually adequate with additional coverage only for known risk factors (e.g., prior colonization with MRSA). For pancreas transplantation, perioperative prophylaxis against yeasts with fluconazole is commonly used, remembering the interactions between azole antifungal agents and calcineurin inhibitors and sirolimus (levels may be increased significantly).

Notable by their absence in the first month after transplantation are opportunistic infections, even though the daily doses of immunosuppressive drugs are at their highest during this time. The implications of this observation are important: The net state of immunosuppression is not great enough to support the occurrence of opportunistic infections unless an exposure has been excessive; this observation suggests that it is not the daily dose of immunosuppressive drugs that is of importance but rather the sustained administration of these drugs, the area under the curve, in determining the net state of immunosuppression. Thus, the occurrence of a single case of opportunistic infection in this period should trigger an epidemiological investigation for an environmental hazard.

Phase Two: 1 to 6 Months after Transplantation

Infection in the transplant recipient 1 to 6 months after transplantation has one of three causes:

1. Lingering infection from the perisurgical period, including relapsed *C. difficile* colitis, inadequately

TABLE 38-6 Renal Transplantation Antimicrobial Prophylaxis Protocols at the Massachusetts General Hospital, Boston

A. Anti-PCP and General Antibacterial Prophylaxis

Background: Low dose TMP-SMX prophylaxis (in adults: 1 single strength per day orally) is well-tolerated and essentially eradicates *Pneumocystis* infection from this patient population; it also helps prevent other infections such as urinary tract infection, nocardiosis and listeriosis, toxoplasmosis, and a variety of gastrointestinal and pulmonary infections.

Regimen: One single strength TMP-SMX tablet (containing 80 mg trimethoprim, 400 mg sulfamethoxazole) orally at bedtime for a minimum of 4-6 months posttransplantation. One double strength tablet three times a week may also be used. Patients infected with CMV, with chronic rejection, or recurrent infections may be maintained on longer or lifelong prophylaxis. For those patients proven to not tolerate TMP-SMX, alternative regimens include: 1) a combination of atovaquone 1500 mg orally with meals once daily, plus levofloxacin (or equivalent fluoroquinolone without antianaerobic spectrum) 250 mg once daily to help prevent other non-PCP infections; 2) pentamidine (300 mg IV or inhaled every 3-4 weeks); and 3) Dapsone (100 mg orally daily). Each of these agents has toxicities that must be considered, including hemolysis in G6PD-deficient hosts with dapsone and methemoglobinemia. None of these alternative programs offer the same broad protection of TMP-SMX.

B. Herpes Group Virus Prevention

The human herpes viruses ([CMV], [HSV-1 and HSV-2], [EBV], [VZV], [HHV-6], [HHV-7] and [HHV-8/Kaposi sarcoma-associated herpes virus]) are among the most important causes of infectious disease morbidity and mortality in the transplant recipient. Different regimens are determined by the clinical risk, the major determinants of which are the past experience of donor and recipient with the virus (as defined by the presence or absence of circulating antibody prior to transplant) and the nature of the immunosuppressive therapy.

Regimen for Herpes prophylaxis

CYTOLYTIC TRANSPLANT (THYMOGLOBULIN, OKT3, ETC.)	DONOR CMV ANTIBODY	RECIPIENT CMV ANTIBODY	PROPHYLAXIS	MONITORING WITH CMV ANTIGENEMIA
Yes	+	−	Valcyte × 6 mos	Team may wish to monitor if clinically indicated by symptoms
	−	+		
	+	+		
	−	−		
	+	−	ACV/Famvir/ValACV 6 mos*	
No	−	+	Valcyte × 3 mos	Team may wish to monitor if clinically indicated by symptoms
	−	+		
	+	+		
	−	−		
			ACV/Famvir/ValACV 3 mos*	

GENERIC NAME	TRADE NAME	GFR >60	GFR 40-59	GFR 25-39	GFR 10-24
Valganciclovir	Valcyte	900 mg a day	450 mg a day	450 mg every 2 days	450 mg twice a week
Acyclovir*	Zovirax	400 mg po tid[35]	400 mg po bid[35]	400 mg po bid[35]	200 mg po tid[35]
Famciclovir*	Famvir	500 mg po q day	250 mg a day	250 mg a day	250 mg every 2 days
Valacyclovir*	Valtrex	500 mg po bid[35]	500 mg po q day[35]	500 mg po q day[35]	500 mg po every 2 days[35]

C. Anti-*Candida* Prophylaxis

Prevention of mucocutaneous infection can be accomplished with oral clotrimazole (may increase calcineurin inhibitor levels) or nystatin 2 to 3 times per day at times of steroid therapy or in the face of antibacterial therapy; we usually give for the first 3 to 5 days after transplantation. Fluconazole (at a dose of 200-400 mg/day for 10-14 days) is used in the treatment of prophylaxis failures. Routine prophylaxis with fluconazole for 30 days is used for pancreas transplants.

*Note: Not approved by the U.S. Food and Drug Administration at these doses.
ACV, acyclovir; *CMV*, cytomegalovirus; *EBV*; Epstein-Barr virus; *GFR*, glomerular filtration rate; *HHV*, human herpes virus; *HSV*, herpes simplex viruses; *PCP*, *Pneumocystis jiroveci* pneumonia; *TMP-SMX*, trimethoprim-sulfamethoxazole; *VZV*, varicella-zoster virus.

treated pneumonia, or infection related to a technical problem (e.g., urine leak, lymphocele, hematoma). Fluid collections require drainage for treatment.

2. Viral infections, including CMV, HSV, shingles (VZV), human herpesvirus 6 or 7, EBV, relapsed hepatitis (HBV, HCV), and HIV. These viruses are unique: lifelong infection; tissue-associated (often transmitted with the allograft from seropositive donors); immunomodulating—systemically immune suppressive; and, potentially, predisposing to graft rejection. It is also notable that the herpesviruses are prominent because of the attenuated ability of T-cells to control these infections. Among the other viral pathogens of this period that must be included are BK polyomavirus in association with allograft dysfunction, and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus, metapneumovirus). The suppression of antibody production (e.g., using tacrolimus and mycophenolate mofetil or with lymphopenia) may predispose to other infections.
3. Opportunistic infection due to *P. jiroveci, Listeria monocytogenes, Toxoplasma gondii, Nocardia* species, *Aspergillus* species, and other agents.

In this period, the stage is also set for the emergence of a subgroup of patients, the "chronic ne'er-do-wells"—individuals who require higher than average immune suppression to maintain graft function or who have prolonged untreated viral infections and other opportunistic infections, predicting long-term susceptibility to many other infections (third phase, discussed later). Such individuals may merit prolonged (lifelong) prophylaxis (antibacterial or antiviral, or both) to prevent life-threatening infection.

The specific opportunistic infections that occur reflect the specific immunosuppressive regimen used and the presence or absence of immunomodulating viral infection. Viral pathogens (and rejection) are responsible for the majority of febrile episodes that occur in this period. During this period, anti-CMV strategies and trimethoprim-sulfamethoxazole prophylaxis are effective in decreasing the risk of infection. Trimethoprim-sulfamethoxazole prophylaxis eliminates *P. jiroveci* pneumonia (PCP) and reduces the incidence of urinary tract infection and urosepsis, *Listeria monocytogenes* meningitis, *Nocardia* species infection, and *T. gondii* infection.

Phase Three: More than 6 to 12 Months after Transplantation

Transplant recipients who are more than 6 months past the procedure can be divided into three groups in terms of infection risk.

The first group consists of the majority of transplant recipients (70%-80%) who had a technically good procedure with satisfactory allograft function, reduced and maintenance immunosuppression, and absence of chronic viral infection. These patients resemble the general community in terms of infection risk, with community-acquired respiratory viruses constituting their major risk.

The second group (~10% of patients) suffers chronic viral infection, which, in the absence of effective therapy, will lead inexorably to either end organ damage (e.g., BK polyomavirus nephropathy, cryoglobulinemia, or cirrhosis from HCV; HBV being relatively well managed at present) or malignancy (posttransplantation lymphoproliferative disease [PTLD] due to EBV or anogenital cancer due to papilloma viruses).

The third group of patients (~10% of all recipients) has less than satisfactory allograft function and requires excessive amounts of immunosuppressive therapy for recurrent graft rejection. This may be associated with chronic viral infection. This is the subgroup of transplant recipients, often termed the "chronic ne'er-do-wells," who are at highest risk for opportunistic infection with such pathogens as *P. jiroveci, L. monocytogenes, Nocardia asteroides,* and *Cryptococcus neoformans*. It is our practice to give these patients lifetime maintenance trimethoprim-sulfamethoxazole prophylaxis and to consider the use of fluconazole prophylaxis. Also, this group is susceptible to organisms more often associated with immune dysfunction of acquired immune deficiency syndrome (AIDS) (*Bartonella, Rhodococcus, Cryptosporidium,* and *Microsporidium* species) and invasive fungal pathogens (*Aspergillus, Zygomycetes,* and the *Dematiaceae* or pigmented molds). Minimal clinical signs or symptoms merit careful evaluation in these vulnerable high-risk individuals.

ASSESSMENT OF INFECTIOUS DISEASE RISK IN RECIPIENT AND POTENTIAL DONOR BEFORE TRANSPLANTATION

Guidelines for pretransplantation screening have been the subject of several recent publications including a consensus conference of the Immunocompromised Host Society (ICHS), the American Society for Transplantation (AST) Clinical Practice Guidelines on the evaluation of renal transplantation candidates, and the American Society of Transplant Physicians (ASTP) Clinical Practice Guidelines on the evaluation of living renal transplant donors.[2–9]

The Transplant Donor

Deceased Donor Evaluation

Time constraints are the critical feature in screening deceased donors. A useful organ may be procured and implanted before some microbiological assessments have been completed. Thus, major infections must be excluded and appropriate cultures and stored samples obtained for future reference. As a result, bacteremia or fungemia may not be detected until after the transplantation has occurred. Such infections have not generally resulted in transmission of infection as long as the infection has been adequately treated or covered by the routine antibiotic prophylaxis.[6,7] In recipients of tissues from 95 bacteremic donors, a mean of 3.8 days of effective therapy post-transplantation appeared adequate to prevent transmission; longer courses of therapy in the recipient are preferred, targeting known potential pathogens from the donor.[10] Bacterial meningitis must also be treated with antibiotics that penetrate the cerebrospinal fluid (CSF) before procurement. Similarly, because of the limited time for testing, certain acute infections (HIV, HBV, or HCV) may be undetected in the "window" period prior to antibody formation, and many organ procurement organizations are using viral nucleic acid testing to further decrease risk of infection and expand the donor pool.[8,9] The donor's clinical, social, and medical histories are essential in reducing the risk of such infections. The extent of therapy needed for focal infections in the donor outside the procured organs remains unresolved. Major exclusion criteria for donors are outlined in Table 38-4.

Living Donor Evaluation

The differences in screening of the living donor and the cadaver donor are largely based on the different time frames during which this screening takes place. The living donor procedure should be considered elective, thus, the evaluation should be completed and infections treated prior to such procedures. An interim history must be taken at the time of surgery to assess the presence of new infections since the initial donor evaluation. Intercurrent infections (flulike illness, headache, confusion, myalgia, and cough) might be the harbinger of important infection (West Nile Virus, severe acute respiratory syndrome [SARS], rabies, *Trypanosoma cruzi*). Live donors undergo a battery of serological tests (see Table 38-3) and an evaluation for latent TB and, if indicated, a chest radiograph. The testing must be individualized, based on unique risk factors and exposures. Of particular importance to the renal transplant recipient is the exclusion of urinary tract infection.

Special Considerations in Organ Procurement

Mycobacterium tuberculosis

Transmission of donor *M. tuberculosis* represented approximately 4% of reported posttransplantation TB cases in a review of 511 patients by Singh and colleagues.[11] Active

disease should be excluded in purified protein derivative (PPD) positive donors, including chest radiograph, sputum cultures, and chest computed tomography (CT), if the chest radiograph is abnormal. Urine AFB cultures may be useful in the PPD-positive kidney donor. Isoniazid prophylaxis of the recipient should be considered for untreated, PPD-positive donors, especially with donors who are from endemic regions, who use a high-dose steroid regimen, or who are from high-risk social environments.[12]

Chagas Disease (*T. cruzi*)

This parasitic disease has been transmitted by transplantation in endemic areas and recently in the United States,[2] more commonly after heart transplantation, although it can be transmitted with other organs and blood products. Schistosomiasis and infection by *S. stercoralis* are generally recipient-derived problems.

Viral Infections other than Cytomegalovirus

Viral infections are the most common cause of donor-derived infection and can lead to significant graft dysfunction, morbidity, and mortality. Standard pretransplantation testing includes a panel for numerous viruses; many other unsuspected viruses, including zoonotic viruses, have been unwittingly transmitted during organ transplantation.[10] Donors who are considered high-risk are being used more frequently as a means to expand the organ pool. The transplant team should discuss the risks and benefits with each recipient and include this information in the informed consent. Posttransplantation testing with nucleic acid testing should be done 1 to 3 months after transplantation; serological testing has a higher false-negative rate.

Most adult donors are infected with latent EBV. The risk for PTLD is greatest in the EBV seronegative recipient of an EBV seropositive allograft. PTLD is most common in pediatric transplant recipients and in adults coinfected with active CMV or on higher levels of immune suppression. Monitoring after transplantation should be considered for at-risk individuals, using a quantitative, molecular assay (e.g., polymerase chain reaction [PCR]) for EBV.

Hepatitis B surface antigen (HBsAg) and HBV core antibody (HBcAb) are used to screen for HBV, with HBsAb positivity indicating either vaccination or prior infection. The HBsAg negative, HBcAb-immunoglobulin G (IgG) positive donor may have viral DNA in the liver (or maybe be a false-positive) but may be appropriate as a donor.[11,12] Quantitative molecular assays for HBV can be obtained after transplantation for monitoring. HBV vaccination of the recipient prior to transplantation may help protect them against active disease after receiving an HBcAb positive organ. Of note, HBcAb-positive recipients are at higher risk for HBV reactivation after renal transplantation and should be monitored or possibly given antiviral medication.[13]

HCV infection will generally progress more rapidly with immune suppression. HCV seropositive renal transplant candidates are more likely to develop cirrhosis and complications of liver failure. Seropositive donors are usually deferred, except occasionally in the setting of a seropositive recipient with HCV genotype 1 (the other genotypes have less risk of serious illness, and superinfection with genotype 1 is likely to cause worse disease).

HIV-infected donors have not been used except occasionally for HIV infected recipients. The progression of disease is rapid and outweighs the benefits of transplantation. Donors may be excluded based on historic evidence of high-risk behavior for HIV infection.[14] The use of nucleic acid testing prior to transplantation may help us expand the donor pool.[8,9]

Human T lymphotropic virus I (HTLV-I) is endemic in the Caribbean and parts of Asia (Japan) and can progress to HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) or to adult T-cell leukemia/lymphoma (ATL).[15] HTLV-II is similar to HTLV-I serologically but is less clearly associated with disease. Use of organs from such donors is generally avoided, although not all organ procurement organizations test for this virus; it is not known if immunosuppression has an impact on risk of progression to leukemia/lymphoma. Progression to ATL after use of seropositive living donor organs has been reported.[15]

West Nile virus (WNV) is a flavivirus associated with viral syndromes and meningoencephalitis and may be transmitted by blood transfusion and organ transplantation.[16] Routine screening of donors is done by some organ procurement organizations in endemic areas. Donors with unexplained changes in mental status or recent viral illness with neurological signs should be avoided.

Recipient Screening

The pretransplantation period is useful for a thorough travel, animal, and environmental and exposure history; updating immunizations; and counseling of the recipient regarding travel, food, and other infection risks. Ongoing infection must be eradicated prior to transplantation. Two forms of infection pose a special risk:

1. Active bacterial infections: Bloodstream infections may be related to vascular access, including that for dialysis and pneumonia, which puts the patient at high risk for subsequent lung infection with nosocomial organisms. Infected ascites or peritoneal dialysis fluid must also be cleared prior to surgery. Urinary tract infection (UTI) must be eliminated prior to transplantation with antibiotics with or without nephrectomy. Similarly, skin disease that threatens the integrity of this primary defense against infection should be corrected before transplantation, even if doing so requires the initiation of immunosuppression prior to transplantation (e.g., the initiation of immune suppression to treat psoriasis or eczema). Finally, the history of more than one episode of diverticulitis should initiate an evaluation to determine whether sigmoid colectomy should be carried out prior to transplantation.
2. Tuberculosis: The incidence of reactivation disease due to *M. tuberculosis* is far higher in the transplant recipient than in the general population. Patients with end-stage renal disease are more likely to be anergic and have a false-negative PPD. In a cohort of 118 subjects on hemodialysis, 41 (35%) were PPD-positive and 77 (65%) were negative, of which 62 (81%) were anergic.[17] The newly developed interferon-gamma-based QuantiFERON-TB Gold test (Cellestis, Chadstone, Victoria, Australia) may be helpful in diagnosing some additional cases of latent tuberculosis in this setting, and may help distinguish those who have true latent TB from those who

are PPD positive due to prior vaccination with Bacille Calmette-Guerin (BCG). Recent work suggests that for optimal diagnostic accuracy, this test should be done before, rather than after, hemodialysis.[18] Active tuberculosis must be treated prior to transplantation. Latent tuberculosis should be treated either before or at the time of transplantation. The major antituberculous drugs are potentially hepatotoxic, and significant drug interactions are common between the antituberculosis agents and the agents of immune suppression (especially the rifamycins).

Pretransplantation screening for other latent infections such as *Strongyloides*, *Schistosoma*, *Coccidioides*, and *Histoplasma* in recipients with the right epidemiology may allow for the clinical team to target prophylaxis more effectively, or reach a diagnosis more rapidly. The pretransplantation evaluation may also allow for better vaccination, such as in those who are seronegative for hepatitis A and B, mumps, measles, rubella, and varicella.

SELECTED INFECTIONS OF IMPORTANCE

General Considerations

The spectrum of infection in the immunocompromised host is quite broad. Given the toxicity of antimicrobial agents and the need for rapid interruption of infection, early, specific diagnosis is essential in this population. The need for invasive diagnostic tools cannot be overemphasized. Advances in diagnostic modalities (CT or magnetic resonance imaging [MRI] scanning and molecular microbiological techniques) may greatly assist in this process. Given the diminished immune responses of the host and the frequency of multiple simultaneous processes, invasive diagnosis is often the best method for optimal care. The initial therapy may, by necessity, be broad with a rapid narrowing of the antimicrobial spectrum as data become available. Reduction in the intensity of immune suppression is a cornerstone of treatment of active infection, balancing risks of the infection with graft rejection. The selection of the specific agent to reduce may depend upon the organisms isolated. Similarly, reversal of some immune deficits (neutropenia, hypogammaglobulinemia) may be possible with adjunctive therapies (colony stimulating factors or intravenous immunoglobulin). Viral coinfection (CMV, EBV) is common and merits additional therapy.

Viral Pathogens

Cytomegalovirus

CMV is the single most important pathogen in transplant recipients and has a variety of direct and indirect effects.[4,19] The direct effects include:

- Fever and neutropenia syndrome with possible hepatitis, nephritis, leukopenia, and/or thrombocytopenia
- Pneumonia
- Gastrointestinal invasion with colitis, esophagitis, gastritis, ulcers, bleeding, or perforation
- Hepatitis, pancreatitis, chorioretinitis

With the exception of chorioretinitis, the direct clinical manifestations of CMV infection usually occur 1 to 4 months after transplantation in the absence of prophylaxis; chorioretinitis is rare after renal transplantation and usually does not begin until later in the transplantation course.

The *indirect effects* of active CMV disease are very important; this term describes the effects of CMV on the host immune system and sequelae thereof. CMV disease produces a profound suppression of a variety of host defenses, resulting in an increase in the net state of immunosuppression, further predisposing the host to secondary invasion by such pathogens as *P. jiroveci*, *Candida* and *Aspergillus* species, and some bacterial infections.[20] CMV also contributes to the risk for graft rejection, PTLD, human herpesvirus 6 (HHV-6), and human herpesvirus 7 (HHV-7) infections.

The association between kidney rejection and CMV infection in renal allograft recipients was demonstrated more than a decade ago.[21,22] Seronegative recipients of renal transplants from seropositive donors showed a 50% reduction in organ rejection when given antiviral CMV prophylaxis compared to placebo.[23] CMV prophylaxis is associated with less rejection and significant improvements in graft and patient survival in donor-positive, recipient-negative (D+/R-) deceased-donor kidney recipients at 3 years.[24]

The mechanisms by which CMV causes allograft damage are complex and remain unknown. Possible mechanisms include increased antigen processing and presentation associated with the major histocompatibility complex (MHC); altered expression of proinflammatory growth factors, chemokines, and cytokines; altered T-cell subsets; upregulation of proinflammatory adhesion molecules; modulation of the nitric oxide synthase pathway; induction of intracellular reactive oxygen species in vascular smooth muscle cells; and procoagulant activity via antithrombin III and fibrinogen.[4,25–27]

Patterns of Transmission Transmission of CMV in the transplant recipient occurs in one of three patterns: primary infection, reactivation infection, and superinfection.[4]

Primary infection occurs when seronegative individuals receive grafts from latently infected, seropositive donors (D+/R-), with subsequent activation of the virus and systemic dissemination after transplantation. Between 40% and 50% of these patients experience direct infectious disease manifestations of CMV while the majority are viremic, often without symptoms. Primary CMV infection may also occur in seronegative individuals after transfusion or sexual contacts in the community; such disease may be severe.

In reactivation infection, seropositive individuals reactivate endogenous virus after transplantation (donor seropositive or seronegative, recipient seropositive [D+/R+ or D-/R+]). When conventional immunosuppressive therapy is used (without antilymphocyte antibody treatment), about 10% to 15% experience direct infectious disease syndromes; higher rates (up to 50%) are seen with the use of induction antilymphocyte therapy.

Superinfection with CMV also can occur. Various genotypes of CMV exist; in a recent survey, gB1 was the predominant single genotype (50.4%), followed by gB2 (21%), gB3, (9%), and gB4 (3%), and mixed-genotype infections were seen in 17% with much higher viral loads noted.[28] The viral genotype or genotypes causing active disease in the setting of an allograft from a seropositive donor transplanted into a seropositive recipient remains to be elicited.

Pathogenesis Control of CMV infection is via MHC-restricted, virus-specific, cytotoxic T lymphocyte response

controlled by CD4+ lymphocytes. Seroconversion has been used as a predictor for the development of host immunity. QuantiFERON-CMV is an emerging diagnostic assay for the detection of interferon (IFN)-gamma in response to CMV CD8+ T-cell epitopes and may be a useful clinical tool for monitoring the immune response in immunosuppressed patients during therapy.[29] The major effector for activation of virus is the nature of the immunosuppressive therapy being administered. The antilymphocyte antibodies, both polyclonal and monoclonal, are direct activators of viral infection (mimicking the alloimmune response) and also provoke the elaboration of tumor necrosis factor (TNF) and the other proinflammatory cytokines that enhance viral replication. Cyclosporine, tacrolimus, sirolimus, and prednisone (other than pulse doses) have limited ability to reactivate latent CMV while azathioprine, mycophenolate, and cyclophosphamide are moderately potent in terms of promoting viral reactivation. Allograft rejection is a major stimulus for CMV activation and vice versa. CMV infection has been linked to a diminished outcome of renal and other allografts, as described above.

Diagnosis Careful clinical management of CMV, both prevention and treatment, is of great importance for the transplant recipient. CMV cultures are generally too slow and insensitive for clinical use. A positive CMV culture (or shell vial culture) derived from respiratory secretions or urine is of little diagnostic value, since many patients secrete or shed CMV in the absence of invasive disease. Serological tests are useful prior to transplantation to predict risk but are of little value after transplantation in defining clinical disease (this statement includes measurements of anti-CMV IgM levels). Seroconversion in transplantation is generally delayed and thus not useful for clinical diagnosis. Seroconversion to CMV is evidence that that the patient has been exposed to CMV and has developed some degree of immunity. Serologies may be confounded by recent administration of blood products. The demonstration of CMV inclusions in tissues in the setting of a compatible clinical syndrome is the gold standard for diagnosis.

Two types of quantitative assays have been developed: the nucleic-acid based molecular assays and the antigen detection assays. The molecular assays are highly specific and sensitive for the detection of viremia. The antigenemia assay is a semiquantitative fluorescent assay in which circulating neutrophils are stained for CMV early antigen (pp65), which is taken up nonspecifically as a measure of the total viral burden in the body. The molecular and antigenemia assays cannot be directly compared; caution should be used when comparing similar assays done in different laboratories, as there can be significant interlaboratory variation. Either assay can be used in management. The highest viral loads (or antigenemias) are often associated with tissue-invasive disease, with lower levels found with asymptomatic CMV infection, and variable loads in the CMV syndrome.

Quantitation of the intensity of CMV infection has been linked to the risk for infection in transplant recipients.[30] The advent of quantitative assays for the diagnosis and management of CMV infection has allowed noninvasive diagnosis in many patients with two important exceptions: neurological disease, including chorioretinitis; and gastrointestinal disease, including invasive colitis and gastritis. In these syndromes, the CMV assays may be negative and invasive (biopsy) diagnosis may be needed.

The central role of assays is illustrated by the approach to prevention of CMV (see Table 38–6). The schedule for screening is linked to the risk for infection. Thus monthly screening is performed in the high risk patient after the completion of prophylaxis to screen for late-onset infection for 3 to 6 months. In the patient being treated for CMV infection, the assays provide an end point (zero positivity) for therapy and the initiation of prophylaxis. In the event that clinical resistance develops while on appropriate treatment with ganciclovir, genotyping by molecular diagnostic assay is commercially available with a rapid turn-around time (especially compared to previous culture-based assays) and may provide further guidance as to the optimal therapy.[30]

Cytomegalovirus Prevention Prevention of CMV infection must be individualized for immunosuppressive regimens and the patient. Two strategies commonly used for CMV prevention are the following: 1) universal antiviral prophylaxis; and 2) preemptive therapy. Universal prophylaxis involves giving antiviral therapy to all at-risk patients beginning at or immediately posttransplantation for a defined time period. In preemptive therapy, quantitative assays are used to monitor patients at predefined intervals (often every week) to detect early disease. Positive assays result in therapy. Preemptive therapy incurs extra costs for monitoring and coordination of outpatient care while reducing the cost of drugs and the inherent toxicities. Universal prophylaxis has the possible advantage of preventing not only CMV infection during the period of greatest risk, but also diminishing infections due to HHV6, HHV7, and EBV. Further, the indirect effects of CMV (i.e., graft rejection, opportunistic infection) may also be reduced by routine prophylaxis. In practice, neither strategy is perfect. Both breakthrough disease and ganciclovir resistance have been observed in both approaches.

Given the risk for invasive infection, patients at risk for primary infection (CMV D+/R-) tend to be given prophylaxis for 3 to 6 months after transplantation. We use 6 months of prophylaxis in patients receiving lytic antilymphocyte antibodies such as thymoglobulin. Other groups are candidates for preemptive therapy if an appropriate monitoring system is in place and patient compliance is good. Prophylaxis is achieved with 50% of the therapeutic dose of ganciclovir or valganciclovir (corrected for renal function). The dose of antiviral prophylaxis should not be reduced for neutropenia.

Treatment The standard of care for treating CMV disease had been 2 to 3 weeks of intravenous ganciclovir (5 mg/kg twice daily, with dosage adjustments for renal dysfunction). New data suggests that oral valganciclovir, which has a bioavailability of 60%, may be used to treat mild to moderate disease.[31,32] Relapse does occur, primarily in those not treated beyond the achievement of a negative quantitative assay. Therefore, we treat intravenously until viremia has been cleared and follow it with prophylaxis with 1 to 3 months of oral ganciclovir (1 g two or three times daily) or valganciclovir (based on creatinine clearance). This approach has resulted in rare symptomatic relapses and appears to prevent the emergence of antiviral resistance.

A number of issues remain. Some relapses occur in gastrointestinal (GI) disease because the blood assays used to follow disease are not reliable in this setting. Thus, repeat

endoscopy should be considered to assure the clearance of infection. The optimum dosing of valganciclovir for prophylaxis in renal transplant recipients is also unclear. Many centers use 450 mg/day orally (given reduced creatinine clearance), although the U.S. Food and Drug Administration (FDA) has approved a dose of 900 mg/day. It may be worth measuring the creatinine clearance to ensure appropriate dosing. We have seen cases of resistance with better-than-expected renal function and lower doses of valganciclovir.

Alternative therapies are available in intravenous form only. These include foscarnet and cidofovir. Foscarnet has been used extensively for therapy of CMV in AIDS patients. It is active against most ganciclovir-resistant strains of CMV. We sometimes use combination therapy (ganciclovir and foscarnet) for such individuals, given the toxicities of each agent and the antiviral synergy demonstrated.[33] Cidofovir has been used in renal transplantation recipients, often with nephrotoxicity; isolates that are resistant to ganciclovir are more likely to also be resistant to cidofovir than foscarnet. Both foscarnet and cidofovir may exhibit synergistic nephrotoxicity with calcineurin inhibitors. A newer class of agents (leflunomide) has been approved for immune suppression and treatment of rheumatological diseases and may have useful activity against CMV (and possibly BK polyomavirus).[34]

Varicella Zoster

Most adult renal transplant recipients were previously infected with VZV and are at risk for reactivation infection (shingles or zoster).[35] Occasional cases of widely disseminated, life-threatening disease are seen. Viral prophylaxis in the first 3 to 6 months after solid organ transplantation may help protect transplant recipients during their most vulnerable time. Previously nonimmune recipients are at risk for severe community-acquired primary disease. Both the varicella and zoster vaccines are live viral vaccines that are generally contraindicated in immunosuppressed hosts.[36]

Diagnosis The rashes of HSV-1/2 and varicella zoster can be clinically similar in certain locations, and it is important to distinguish between them. Skin scrapings or biopsies may be sent for cultures or immunohistochemistry analysis, or both, which can identify the specific virus. Serology is not helpful in the acute setting, except to confirm that someone may have reactivation disease.

Treatment Treatment of HSV-1/2 infection involves lower doses of renally-adjusted acyclovir, while zoster requires higher doses of either valacyclovir (1 g three times a day, renally adjusted) or intravenous acyclovir for disseminated or significant multi-dermatomal disease. Post-herpetic neuralgia can be very debilitating and may require further medications; guidelines on management can be helpful.[37] In general, acute disease with varicella zoster may serve to "vaccinate" the host. The live, viral vaccine has no part in acute management, nor should it be given to immunocompromised hosts.

Epstein-Barr Virus

EBV is a ubiquitous herpesvirus with which the majority of adults are infected. EBV primarily infects B lymphocytes. In immunosuppressed transplant recipients, primary EBV infection (and relapses in the absence of antiviral immunity) causes a mononucleosis-type syndrome, generally presenting as a lymphocytosis (B-cells) with or without lymphadenopathy or pharyngitis. Meningitis, hepatitis, and pancreatitis may also be observed. Remitting-relapsing EBV infection is common in children and may reflect the interplay between evolving antiviral immunity and immune suppression. This syndrome may suggest relative overimmune suppression and may lead to PTLD,[38] since EBV plays a central role in the pathogenesis of PTLD. The most clearly defined risk factor for PTLD is primary EBV infection that increases the risk for PTLD by 10-fold to 76-fold. PTLD may occur, however, in the absence of EBV infection or in seropositive patients. Posttransplantation non-Hodgkin lymphoma (NHL) is a common complication of solid organ transplantation. Lymphomas comprise up to 15% of tumors among adult transplant recipients (51% in children) with mortality of 40% to 60%. Many deaths are associated with allograft failure after withdrawal of immune suppression during treatment of malignancy. Compared to the general population, PTLD has increased extranodal involvement, poor response to conventional therapies, and poor outcomes. The spectrum of disease ranges from benign polyclonal, B-cell infectious mononucleosis like disease to malignant, monoclonal lymphoma.[38] The majority is of B-cell origin, although T-cell, natural killer-cell and null cell tumors are described. It should be noted that T-cell PTLD has been demonstrated in allografts and confused with graft rejection or other viral infection. Late PTLD (more than 1-2 years after transplantation) is more often EBV-negative in adults.

The clinical presentations of EBV-associated PTLD are protean and may include:

1. Unexplained fever
2. A mononucleosis-type syndrome, with fever, malaise, with or without pharyngitis or tonsillitis (occasionally diagnosed incidentally in tonsillectomy specimens, especially in children); lymphadenopathy may not be observed.
3. Gastrointestinal bleeding, obstruction, perforation
4. Abdominal mass lesions
5. Infiltrative disease of the allograft
6. Hepatocellular or pancreatic dysfunction
7. Central nervous system disease

Diagnosis Quantitative EBV viral load testing is required for the diagnosis and management of PTLD.[39,40] Serological testing is not useful for the diagnosis of acute EBV infection or PTLD in transplantation. Serial assays are more useful in an individual patient than specific viral load measurements. These assays are not standardized and cannot be directly compared between different laboratories. In general, the pathological diagnosis is otherwise similar as for other types of lymphoma. Special immunohistochemistry stains for EBV can sometimes be helpful. Gene rearrangement studies can also be useful, especially for the rarer lymphomas.[39]

Management Clinical management depends on the stage of disease. In the polyclonal form, particularly in children, establishment or augmentation of immune function may suffice to cause PTLD to regress. Reduction of immunosuppression remains the mainstay of first-line treatment; accumulating evidence supports the role of rituximab as second-line therapy with cytotoxic chemotherapy reserved for specific circumstances.[41]

Polyomaviruses

Polyoma viruses have been identified in transplant recipients in association with nephropathy and ureteral obstruction (BK virus, BKV) and in association with demyelinating disease of the brain (JC virus, JCV) similar to that in AIDS.[42–47] Polyoma viruses are small nonenveloped viruses with covalently closed, circular, double-stranded DNA genomes. Adult levels of seroprevalence are 65% to 90%.[48] BK virus appears to achieve latency in renal tubular epithelial cells. JC virus has also been isolated from renal tissues but appears to have preferred tropism for neural tissues.[49] Reactivation occurs with immune deficiency, suppression, and tissue injury (e.g., ischemia-reperfusion).

BK Polyoma Virus Infection BK virus is associated with a range of clinical syndromes in immunocompromised hosts: viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis particularly in recipients of bone marrow transplantation (BMT).[40,41,44,45] Active infection of renal allografts has been associated with progressive loss of graft function (BK nephropathy) in 3% to 10% of renal transplantation patients.[44] This may be referred to as polyoma virus-associated nephropathy (PVAN). BK nephropathy is rarely recognized in recipients of nonrenal organs.[45] The clinical presentation of disease is usually as sterile pyuria, reflecting shedding of infected tubular and ureteric epithelial cells. These cells contain sheets of viruses and are detected by urine cytology as *decoy cells*.[44] Some patients present with diminished renal allograft function or, rarely, with ureteric stenosis and obstruction. In such patients, the etiologies of decreased renal function must be carefully evaluated (e.g., mechanical obstruction, drug toxicity, pyelonephritis, rejection, thrombosis, active infection, or recurrent disease). The choice of treatment is to either increase immune suppression to treat suspected graft rejection or reduce immune suppression to allow the immune system to control infection. Patients with BK nephropathy treated with increased immune suppression have a high incidence of graft loss associated with further reactivation of the BK virus. Reduced immune suppression may stabilize viral activation, but risks graft rejection. Polyoma-associated nephropathy manifested by characteristic histological features and renal dysfunction is found in about 1% to 8% of renal transplant patients.[50]

Risk factors for nephropathy are poorly defined. Hirsch et al.[43,51] found that cellular rejection occurred more commonly in patients with BK nephropathy than in controls. Other studies have implicated high dose immunosuppression (particularly tacrolimus and mycophenolate mofetil),[52] pulse dose steroids, severe ischemia-reperfusion injury, exposure to antilymphocyte antibody therapy, an increased number of human leukocyte antigen mismatches, cadaver renal transplants, and the presence and degree of viremia in the pathogenesis of disease.[44,45] The intensity of immunosuppression is a major risk factor. However, the role of a specific immunosuppressive agent or agents has not been confirmed.[44,45]

Diagnosis The use of urine cytology to detect the presence of infected decoy cells in the urine has approximately 100% sensitivity for BK virus infection but a low (29%) predictive value.[45,53] It is therefore a useful screening tool but cannot establish a firm diagnosis. The use of molecular techniques to screen blood or urine has also been advocated but is more useful in management of established cases (viral clearance with therapy) than in specific diagnosis.[54] Hirsch and colleagues[43] showed that patients with BK nephropathy have a plasma viral load statistically higher (>7700 BK virus copies per ml of plasma, $p < 0.001$) compared to patients without PVAN.

Given the presence of viremia in renal allograft recipients, it is critical to reduce immunosuppression. However, the possible coexistence of acute rejection with BK infection, present in 12% of cases, makes renal biopsy essential for the management of such patients. Drachenberg[50,55] grades the histology of PVAN in three stages based on the degree of inflammation and fibrosis. In stage 1 cytopathic changes are present in the biopsy with minimal or no fibrosis. Stage 2 presents with cytopathic changes and, in addition, various degrees of inflammation and fibrosis. Stage 2 is subdivided into A, B, or C depending on the degree of inflammation/fibrosis: A less than 25%, B 25% to 50%, and C greater than 50%. Finally stage 3, with intensive fibrosis, is indistinguishable from any kind of end-stage kidney disease. Immunostaining for cross-reacting SV40 virus demonstrates patchy staining of viral particles within tubular cells in stages 1 and 2, but not in stage 3.

Treatment The cornerstone treatment of PVAN continues to be reduction/adjustment in the intensity of immunosuppression. Ramos and colleagues[44] and Drachenberg and colleagues[42] have reported an algorithm used at the University of Maryland for early diagnosis and treatment of PVAN. Similarly, Ginevri and colleagues[40] have reported a similar successful protocol used in pediatric patients. It is possible to monitor the response to such interventions using urine cytology (decoy cells) and viral load measures in blood or urine, or both.[45] Regardless of the approach, renal function, drug levels, and viral loads must be monitored carefully.[53]

Additionally several agents with antipolyoma viral activity in vitro have been used to decrease in immunosuppression, including cidofovir in low doses (0.25-1 mg/kg every 2 weeks).[44,45] Significant renal toxicity may be observed with this agent, especially in combination with the calcineurin inhibitors. Other agents include leflunomide, quinolones and intravenous immunoglobulins (IVIG).[56–59] None of these agents are FDA approved for the treatment of PVAN. Additionally, it is difficult to assess the efficacy of these agents since the number of cases published is relatively small, and no prospective randomized control trials have been conducted. Frequently these agents have been used in combination with decreased immunosuppression, and at times together.[56]

Retransplantation has been consistently successful in patients with graft loss due to PVAN, although recurrence of the infection is known to occur. Careful monitoring is warranted in retransplanted patients, particularly if there is evidence of some level of active viral replication.[60,61]

JC Virus and Progressive Multifocal Encephalopathy Infection of the central nervous system by JC polyoma virus (JCV) has been observed uncommonly in renal allograft recipients as progressive multifocal encephalopathy (PML).[62,63] This condition generally presents with focal neurological deficits or seizures and may progress to death following extensive demyelination.[49,63–65] PML may be confused with calcineurin neurotoxicity, and both may respond to a reduction in calcineurin inhibitor levels.[63] PML occurs

almost exclusively in immunocompromised patients. The first case was in 1958, in a patient with chronic lymphocytic leukemia and Hodgkin disease.[49] At present, most of the patients diagnosed with this condition have AIDS.[65–67] Fourteen cases have been described in patients following renal transplantation.[63] Cases have also been described in lung, heart, and liver transplantations.[68–70]

Clinical Presentation The most common presentation in PML includes motor weakness, cognitive abnormalities, and speech and visual field deficits.[64] Cranial nerve accessory deficits have also been reported.[71,72] Seizures have been reported as high as 40% in one study.[73] Among the 14 cases in renal transplantation, nine have died. In the remainder, immunosuppression was reduced or discontinued.[63]

Diagnosis CT of the brain shows lesions in the cerebral white matter.[74] However, cerebral MRI is more sensitive in detecting PML lesions. Typically, they appear as areas of increased intensity in the white matter in T2-weighted MRI scans.[75,76] The CSF in PML patients can be normal or may contain increased protein with a few cells, none of which are diagnostic of PML. JC virus DNA PCR in CSF may be obtained, but is not diagnostic and must be confirmed by brain biopsy.[77,78] The latter reveals multiple asymmetrical foci of demyelination in the white matter with cytopathic astrocytes and characteristic JC particles in the nuclei of the oligodendrocytes.[79]

Differential Diagnosis In renal transplantation patients with neurological abnormalities similar to the ones seen in patients with PML, the differential diagnosis could include cerebral toxoplasmosis, lymphoma, and calcineurin-induced neurotoxicity.[63] Characteristic CT and MRI features and cerebral biopsy with SV40 immunostaining help confirm the diagnosis.[74–76]

Treatment Treatment with highly active antiretroviral therapy HAART in HIV patients has been beneficial in treating PML.[78,80,81] In patients with renal transplants, despite the known anti-JC polyoma effect in vitro of cidofovir,[82,83] cytosine arabinoside,[84,85] retinoic acid, and IFN-alpha, none of these compounds have been proven to be clinically effective. Koralnik and associates[86] have shown that JC virus-specific cytotoxic T lymphocytes may be promising in controlling JC viral replication and the progression of the disease. At the present time, modulation of immunosuppression is the only reliable method of treatment available.[63] Early diagnosis with aggressive treatment is of utmost importance in controlling this devastating disease.

Fungal Infections

In addition to the endemic mycoses, transplant recipients are at risk for opportunistic infection with a variety of fungal agents, the most important of which are *Candida* species, *Aspergillus* species, and *C. neoformans*.

Candida Species

Candida is the most common fungal pathogen, with *Candida albicans* and *Candida tropicalis* accounting for 90% of the infections. Mucocutaneous candidal infection (e.g., oral thrush, esophageal infection, cutaneous infection at intertriginous sites, vaginitis) occurs particularly when candidal overgrowth is promoted by the presence of high levels of glucose and glycogen in tissues and fluids (e.g., with poorly controlled diabetes, high-dose steroid therapy) and by broad-spectrum antibacterial therapy. These infections are usually treatable through correction of the underlying metabolic abnormality and topical therapy with clotrimazole or nystatin. More difficult to manage is candidal infection occurring in association with the presence of foreign bodies that violate the mucocutaneous surfaces of the body (e.g., vascular access catheters, surgical drains, and bladder catheters). Optimal management of these infections requires removal of the foreign body and systemic antifungal therapy with fluconazole, an echinocandin, or an amphotericin product.

A special problem in renal transplant recipients is candiduria, even if the patient is asymptomatic. Particularly in individuals with poor bladder function, obstructing fungal balls can develop at the ureteropelvic junction, resulting in obstructive uropathy, ascending pyelonephritis, and the possibility of systemic dissemination. A single positive culture result for *Candida* species from a blood specimen necessitates systemic antifungal therapy, because this finding carries a risk of visceral invasion of more than 50% in this population. Fluconazole (400-800 mg/day, with adjustment for renal dysfunction), because of its better safety profile, is usually used as initial therapy, unless the patient is critically ill or has a fluconazole-resistant species (e.g., *Candida glabrata* or *Candida krusei*). In these instances, therapy is with an echinocandin or amphotericin B, usually in a lipid preparation. Flucytosine may be useful as an adjunctive therapy in resistant infections but must be guided by drug levels and attention to hematopoietic toxicity.

Aspergillus Species

Invasive aspergillosis is a medical emergency in the transplant recipient, with the portal of entry being the lungs and sinuses in more than 90% of patients and the skin in most of those remaining. Two species, *Aspergillus fumigatus* and *Aspergillus flavum*, account for most of these infections, although amphotericin-resistant isolates (*Aspergillus terreus*) are occasionally recognized. The pathological hallmark of invasive aspergillosis is blood vessel invasion, which accounts for the three clinical characteristics of this infection: tissue infarction, hemorrhage, and systemic dissemination with metastatic invasion. Early in the course of transplantation, central nervous system involvement with fungal infection is most often due to *Aspergillus* species, as was exemplified in a recent case report;[87] later after transplantation, other fungi (Zygomycetes, dematiaceous fungi) are increasingly prominent, with a high mortality rate.[88] The drug of choice for *Aspergillus* infection is probably voriconazole, noting the intense interactions between this agent and the calcineurin inhibitors and sirolimus. Liposomal amphotericin is a reasonable alternative, and combination therapies are under study. Of note, surgical debridement is often essential for the successful clearance of such invasive infections.

Central Nervous System Infection and *Cryptococcus neoformans*

Central nervous system (CNS) infection in the transplant recipient is an important differential for the clinician. The spectrum of causative organisms is broad and must be

considered in terms of the timeline for infection in this population. Many infections are metastatic to the CNS, often from the lungs. Thus, a "metastatic workup" is a component of evaluation of CNS lesions, including those due to *Aspergillus, Cryptococcus, Nocardia,* or *S. stercoralis*. Viral infections include cytomegalovirus (nodular angiitis), herpes simplex meningoencephalitis, JCV, PML, and varicella zoster virus. Common bacterial infections include *L. monocytogenes*, mycobacteria, and *Nocardia*. Brain abscess and epidural abscess may be observed with MRSA, while penicillin-resistant pneumococcus and quinolone-resistant streptococci can be problematic. Metastatic fungi include *Aspergillus* and *Cryptococcus* but also spread from sinuses (Mucoraceae), skin (Dematiaceae), and bloodstream (*Histoplasma* and *Pseudallescheria/Scedosporium*, *Fusarium* species). Parasites include *T. gondii. T. cruzi,* and *Strongyloides*. Given the spectrum of etiologies, precise diagnosis is essential. In the proper settings, empiric therapy should "cover" *Listeria* (ampicillin), *Cryptococcus* (fluconazole or amphotericin), and HSV (acyclovir) while awaiting data from lumbar puncture, blood cultures, and radiographic studies. Included in the differential diagnosis are noninfectious etiologies, including calcineurin inhibitor toxicity, aseptic meningitis from trimethoprim/sulfamethoxazole (TMP-SMX), lymphoma, and metastatic cancer. Biopsy may be needed for a firm diagnosis.

Cryptococcus neoformans

The most common presentation of cryptococcal infection is that of an asymptomatic pulmonary nodule, often with active organisms present. In the "chronic ne'er-do-well" patient, pneumonia and meningitis are common with skin involvement at sites of tissue injury (catheters) also being observed. Cryptococcosis should be suspected in transplant recipients present with unexplained headaches (especially when accompanied by fevers), decreased state of consciousness, failure to thrive, or unexplained focal skin disease (which requires biopsy for culture and pathological evaluation) more than 6 months after transplantation. Diagnosis is often achieved by serum cryptococcal antigen detection, but all such patients should have lumbar puncture for cell counts and cryptococcal antigen studies. Initial treatment is probably best with amphotericin and 5-flucytosine followed by high dose fluconazole until the cryptococcal antigen is cleared from blood and CSF. Scarring and hydrocephalus may be observed.

Pneumonia and Pneumonitis

The spectrum of potential pathogens of the lungs in transplantation is too broad for this discussion. As for all infections in transplantation, invasive diagnostic techniques are often necessary in these hosts. The depressed inflammatory response of the immunocompromised transplant patient may greatly modify or delay the appearance of a pulmonary lesion on radiograph. Focal or multifocal consolidation of acute onset will quite likely be caused by bacterial infection. Similar multifocal lesions with subacute to chronic progression are more likely secondary to fungi, TB, or nocardial infections. Large nodules are usually a sign of fungal or nocardial infection, particularly if they are subacute to chronic in onset. Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, are usually caused by viruses (especially CMV) or *P. jiroveci*.[66,67] Additional clues can be found by examining pulmonary lesions for cavitation; cavitation suggests such necrotizing infections as those caused by fungi (*Aspergillus* or *Mucoraceae*), *Nocardia, Staphylococcus,* and certain gram-negative bacilli, most commonly with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[68] CT of the chest is useful when the chest radiograph is negative or when the radiographic findings are subtle or nonspecific. CT also is essential to the definition of the extent of the disease process and the possibility of multiple simultaneous processes (superinfection) and to guide the selection of the optimal invasive technique to achieve microbiological diagnosis.

Pneumocystis jiroveci Pneumonia

The risk of infection with *Pneumocystis* is greatest in the first 6 months after transplantation and during periods of increased immune suppression.[4,66,67] The natural reservoir of infection remains unknown. Aerosol transmission of infection has been demonstrated by a number of investigators in animal models, and clusters of infections have developed in clinical settings, including between HIV-infected persons and renal transplant recipients. Activation of latent infection remains a significant factor in the incidence of disease in immunocompromised hosts. In the solid organ transplant recipient, chronic immune suppression that includes corticosteroids is most often associated with pneumocystosis. Bolus corticosteroids, cyclosporine, or coinfection with CMV may also contribute to the risk for PCP.

In patients not receiving TMP-SMX (or alternative drugs) as prophylaxis, most transplant centers report an incidence of *P. jiroveci* pneumonia of approximately 10% in the first 6 months posttransplantation. There is a continued risk of infection in three overlapping groups of transplant recipients as follows: 1) those who require higher than normal levels of immune suppression for prolonged periods of time due to poor allograft function or chronic rejection, 2) those with chronic CMV infection, and 3) those undergoing treatments that increase the level of immune deficiency, such as cancer chemotherapy or neutropenia due to drug toxicity. The expected mortality due to *Pneumocystis* pneumonia is increased in patients on cyclosporine when compared to other immunocompromised hosts. The hallmark of infection due to *P. jiroveci* is the presence of marked hypoxemia, dyspnea, and cough with a paucity of physical or radiological findings. In the transplant recipient, *Pneumocystis* pneumonia is generally acute to subacute in development. Atypical *Pneumocystis* infection (radiographically or clinically) may be seen in patients who have coexisting pulmonary infections or who develop disease while receiving prophylaxis with second choice agents (e.g., pentamidine or atovaquone).[89] Patients outside the usual period of greatest risk for PCP may present with indolent disease confused with heart failure. In such patients, diagnosis often has to be made by

invasive procedures. A number of patients have been identified with interstitial pneumonitis while receiving sirolimus, especially in the setting of reduced creatinine clearance;[90] the clinical presentation may mimic PCP.

Diagnosis The characteristic hypoxemia of *Pneumocystis* pneumonia produces a broad alveolar-arterial Po_2 gradient. The level of serum lactic dehydrogenase (LDH) is elevated in most patients with *Pneumocystis* pneumonia (>300 international units/ml). However, many other diffuse pulmonary processes also raise serum LDH levels. The fungal marker, 1,3-beta-D-glucan, may be markedly positive with PCP.[91]

Like many of the "atypical" pneumonias (pulmonary infection without sputum production), no diagnostic pattern exists for *Pneumocystis* pneumonia on routine chest radiograph. The chest radiograph may be entirely normal or develop the classical pattern of perihilar and interstitial "ground glass" infiltrates. Microabscesses, nodules, small effusions, lymphadenopathy, asymmetry, and linear bands are common. Chest CT scans will be more sensitive to the diffuse interstitial and nodular pattern than routine radiographs. The clinical and radiographic manifestations of *P. jiroveci* pneumonia are virtually identical to those of CMV. Indeed, the clinical challenge is to determine whether both pathogens are present. Significant extrapulmonary disease is uncommon in the transplant recipient.

Identification of *P. jiroveci* as a specific etiological agent of pneumonia in an immunocompromised patient should lead to successful treatment. A distinction should be made between the diagnosis of *Pneumocystis* infection in AIDS and in non-AIDS patients. The burden of organisms in infected AIDS patients is generally greater than that of other immunocompromised hosts and noninvasive diagnosis (sputum induction) more often achieved. In general, noninvasive testing should be attempted to make the initial diagnosis, but invasive techniques should be used when clinically feasible. The diagnosis of *P. jiroveci* infection has been improved by the use of induced sputum samples and of immunofluorescent monoclonal antibodies to detect the organism in clinical specimens. These antibodies bind both cysts and trophozoites. The cyst wall can be displayed by a variety of staining techniques; of these, the Gomori methenamine-silver nitrate method (which stains organisms brown or black) is most reliable, even though it is susceptible to artifacts. Sporozoites and trophozoites are stained by polychrome stains, particularly the Giemsa stain.

Therapy Early therapy, preferably with TMP-SMX, is preferred. In renal transplant recipients, there may be an elevation of creatinine due to trimethoprim (competing for secretion in the kidney) and the toxicity of sulfa agents for the renal allograft. Hydration and the gradual initiation of therapy may help. Alternate therapies are less desirable but have been used with success, including intravenous pentamidine, atovaquone, clindamycin with primaquine or pyrimethamine, and trimetrexate. Although a reduction in the intensity of immune suppression is generally considered a part of antiinfective therapy in transplantation, the use of short courses of adjunctive steroids with a gradual taper is sometimes used in transplant recipients (as in AIDS patients) with severe respiratory distress associated with PCP.

The importance of preventing *Pneumocystis* infection cannot be overemphasized. Low dose TMP-SMX is the most effective agent for prevention, is well-tolerated, and should be used in the absence of concrete data demonstrating true allergy. Alternative prophylactic strategies, including atovaquone, dapsone, inhaled or intravenous pentamidine, are less effective than TMP-SMX but useful in the patient with significant allergy to sulfa drugs. The advantages of TMP-SMX include increased efficacy, lower cost, the availability of oral preparations, and possible protection against other organisms, including *T. gondii, Isospora belli, Cyclospora cayetanensis, N. asteroides*, and common urinary, respiratory, and gastrointestinal bacterial pathogens. It should be noted that alternative agents lack this spectrum of activity.

Vaccination

Because of concerns about the efficacy of vaccines following transplantation, patients should complete vaccinations at least 1 month before to allow time for an optimal immune response. Pretransplant serologies should include varicella, measles, mumps, and rubella; vaccination for these should be performed at least 1 month, and preferably 3 months, before transplantation for resolution of viremia from live vaccines, and only in patients not actively on immunosuppression. Vaccinations should include routine adult vaccines, including pneumococcal vaccine (if not vaccinated in the last 3-5 years), tetanus booster, hepatitis A, hepatitis B, and varicella zoster (Zostavax) (Table 38-7).[92] After transplantation, influenza vaccination should be performed yearly or as per local guidelines. Live vaccines such as nasal influenza, varicella and varicella zoster, measles, mumps, rubella, yellow fever, smallpox, and oral typhoid are not usually given after solid organ transplantation because of safety concerns. Travel-related vaccines and medical advice should be considered both before and after transplantation.[93] Annually updated recommended schedules and doses for routine vaccinations can be obtained from the United States Centers for Disease Control and Prevention (CDC) at www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm or the CDC Immunization Information Hotline, (800) 232-4636.

A full list of references are available at www.expertconsult.com.

TABLE 38-7 Vaccinations to Consider Prior to Transplantation

MMR
Tdap
Hepatitis B
Hepatitis A
HPV
Pneumococcus
Influenza
Varicella and varicella zoster

MMR, measles/mumps/rubella; *Tdap,* diphtheria/tetanus/pertussi; *HPV,* human papilloma virus.

Chapter 39

NONINFECTIOUS COMPLICATIONS AFTER KIDNEY TRANSPLANTATION

Monica Grafals, M.D., John P. Vella, M.D., F.R.C.P., F.A.C.P., F.A.S.N., and Anil Chandraker, M.D.

Kidney transplantation is the treatment of choice for selected patients with end-stage kidney disease (ESRD) because of improvements in patient survival, quality of life, and reduced long-term health costs.[1,2] Clearly, the success of transplantation is founded upon the use of potent immunotherapies that prevent allograft rejection and permit long-term engraftment. The complex pathophysiological changes that occurred during kidney failure before transplantation are often compounded by complications that are directly induced by suppression of the immune system. As patient and graft survival rates have improved, attention has been directed to strategies that mitigate the relatively high burden of morbidity and mortality. Cardiovascular disease, infection, and malignancy are the dominant causes of mortality after kidney transplantation.[3,4] This chapter will focus on the noninfectious complications that develop after transplantation and their management strategies. Complications range in severity from to those that are relatively minor events to those that are allograft or life threatening.

CARDIOVASCULAR DISEASE

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in dialysis and transplant patients[5] accounting for at least one third of all deaths in transplant recipients[6–9] and remains the most common cause of graft loss.[10] ASCVD before kidney transplantation is three to four times more prevalent in the ESRD compared to the general population and has been shown to be a the single most important predictor of cardiovascular mortality after transplantation.[11] Vanrenterghem and colleagues reexplored this topic in order to define current trends.[12] In a cohort of more than 2000 primary allograft recipients, the incidence of cardiovascular events increased over time. Within 15 years of transplantation, only 47% of surviving patients had not experienced any cardiovascular events. Risk factors associated with cardiovascular complications were male gender, age, hypertension (HTN) before transplantation, longer duration of pretransplantation dialysis, cardiovascular event before transplantation, older era of transplantation, center-specific effect, posttransplant diabetes mellitus, increased pulse pressure after transplantation, use of corticosteroids and azathioprine, lower serum albumin after transplantation, and higher serum triglyceride levels after transplantation. The risk of death was also increased in patients with low or elevated hematocrit, while it was minimal with values of about 38%. Numerous other reports have underscored the prevalence and importance of "traditional" risk factors for ASCVD in transplant recipients.[11,13–19]

In spite of those issues, kidney transplantation has repeatedly been shown to reduce cardiovascular and all-cause

mortality compared to dialysis. For example, Meier-Kriesche and associates[20] compared the cardiovascular death (CVD) rates of more than 60,000 adult first kidney transplant recipients and 67,000 waitlisted patients over the same time period. A progressive decline in CVD rates was seen in the transplant recipients compared to the opposite trend for patients who remained on the waiting list. Even though cardiovascular death rates were higher in the early postoperative period, by 3 months posttransplantation, rates were lower than for dialysis patients.

Nontraditional Risk Factors

So what is it about transplantation that lowers cardiovascular risk? Recently, attention has focused on nontraditional cardiovascular risk factors that are prevalent in patients with chronic kidney disease (CKD) that are not effectively controlled by dialysis. An overview of the impact of traditional and nontraditional risk factors is provided in Figure 39-1. *Oxidative stress* is now known to be an important factor in the pathogenesis of ASCVD in patients with ESRD.[21,22] Uremic oxidative stress is characterized biologically by an increase in lipid peroxidation products and reactive aldehyde groups as well as by retention of oxidized thiols.[23,24] The pathophysiology of oxidative stress in uremia is multifactorial, but the retention of oxidized solute by the loss of kidney function is probably a major contributor. We have evaluated time-dependent changes in biomarkers of oxidative stress before and after living donor transplantation.[25] Pretransplantation levels of the proinflammatory proteins interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), and the oxidative stress markers plasma protein carbonyls and F_2-isoprostanes, were significantly elevated in CKD patients compared to healthy control subjects. There was a rapid and sustained decline in all of these biomarkers after transplantation and by two months posttransplantation levels had reached those of the controls. Cueto-Manzano and colleagues also reported increased levels of inflammatory markers pretransplantation that initially fell posttransplantation and, in the case of CRP, remained low, while levels of TNF-α and IL-6 fell, only to rise by the first posttransplantation year.[26] Ducloux and associates recorded coronary events in 8% of 344 consecutive kidney transplant patients who were free of vascular disease at the time of transplantation.[19] In addition to "traditional" Framingham risk factors, CRP and homocystinemia were found to be independent risk factors for ischemic heart disease events. Sezer and colleagues retrospectively analyzed the predictive role of CRP on the development of chronic allograft dysfunction.[27] No difference was found between the pretransplantation levels of CRP between those transplant recipients who were destined to develop allograft dysfunction and those who were not. However, CRP levels were significantly higher in patients with allograft dysfunction by one month posttransplantation and at the time of diagnosis of allograft dysfunction.

Hypertension

About 70% of transplant recipients are hypertensive.[28] HTN after transplantation is associated with numerous factors that include pretransplantation HTN and cause of primary disease, and posttransplantation factors such as delayed graft function, immunosuppression therapy, rejection, transplant renal artery stenosis, acquired glomerular filtration rate (GFR), chronic immune and nonimmune injury, recurrent or *de novo* allograft glomerulonephritis, and weight gain.[28,29] HTN is a risk factor for premature allograft failure, ASCVD, and death with a functioning graft.

It is known that calcineurin inhibitors (CI) and steroids induce or exacerbate HTN after transplantation. The CIs disrupt the normal balance between endogenous vasodilators and vasoconstrictors leading to afferent arteriolar vasoconstriction and thus HTN. In part, this effect is mediated via activation of the sympathetic nervous system[30,31] and also increased expression of endothelin.[32] Watschinger described the pathogenic role of endothelin in this setting by[33] administering an endothelin receptor antagonist that blunted the

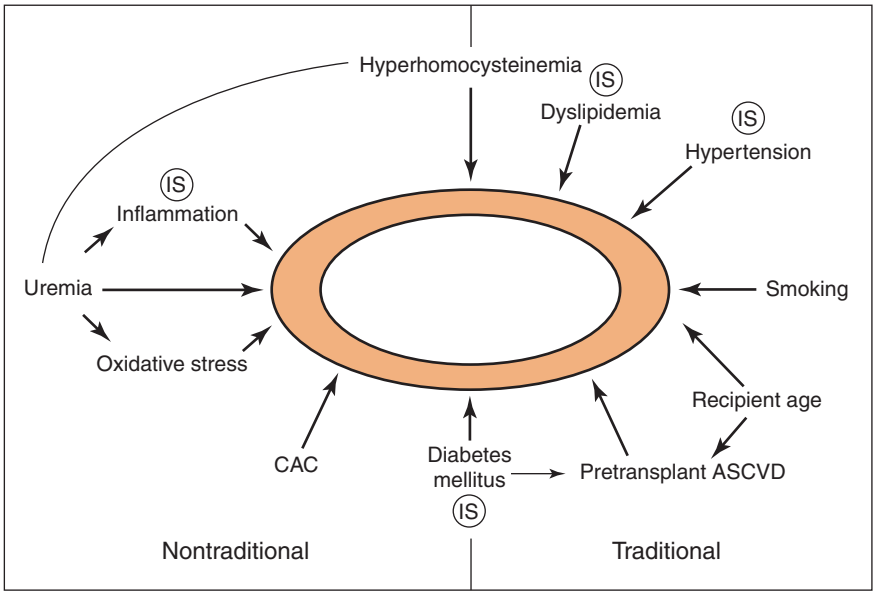


FIGURE 39-1 Pathogenesis of atherosclerosis after kidney transplantation. Numerous processes interplay to induce atherosclerosis after transplantation that include traditional (or Framingham) and nontraditional factors. *ASCVD*, atherosclerotic cardiovascular disease; *CAC*, coronary artery calcification; *IS*, immunosuppression.

rise in blood pressure induced by cyclosporin A (CsA) in vivo. Vasoconstriction is compounded by depressed nitric oxide induced vasodilatory activity.[34] A recent report described a novel mechanism by which CsA causes sodium retention in the thick ascending limb of the loop of Henle leading to HTN.[35]

It should be recognized that not all CIs induce hypertension to the same extent. For example, numerous clinical trials have now shown that tacrolimus is associated with a significantly reduced requirement for medications to control HTN compared to CsA.[36–38] Similarly, ISA 247, a novel CI currently undergoing clinical trials, may also be associated with less hypertension compared to CsA.[39] Hypertension has also been shown to resolve on converting patients from CsA to tacrolimus and to increase again when switched back to CsA treatment.[40] In addition, normal subjects without kidney disease are more likely to develop hypertension when given CsA compared to tacrolimus.[41]

Steroids also elevate blood pressure via mineralocorticoid induced sodium retention. The effects are dose related, and the relatively low doses of steroids currently used after the first 6 to 12 months are thought to have a small impact on blood pressure. Patients with preexisting HTN appear to be more susceptible to this adverse effect of chronic steroid use.[42] Steroids are associated with multiple complications including hypertension, obesity, glucose intolerance, osteoporosis, avascular necrosis, glaucoma, cataracts, myopathy, and neuropsychiatric complications after transplantation.[43] In various older studies, steroid withdrawal was shown to improve blood pressure, glycemic control, and lipid profiles.[44–46] In truth, although steroid avoidance or early steroid withdrawal are now routinely practiced by many centers in the United States, there is no data that indicates such a practice has any beneficial impact on patient or graft survival and.[47,48] Furthermore, such practices have been shown to increase the early rejection rate and may adversely impact long-term graft function in at least some patients groups.[49,50]

Smoking

Smoking remains an important remediable cardiovascular risk factor that is associated in kidney transplant recipients with an increased burden of cardiovascular disease and an increased risk of premature graft failure.[51] In a recent cross-sectional single center study where smoking habits were analyzed it was found that kidney transplantation is a strong incentive for patients to quit.[52] Morphologically, the main allograft lesion associated with smoking is fibrous intimal thickening of small arteries.[53] A recent cross-sectional analysis demonstrated that 76% of the waitlisted patients and 87% of allograft recipients were nonsmokers at the time of investigation.[52] Among the nonsmoking waitlisted patients, only 31% had never smoked, whereas 41% patients of the allograft recipients had never smoked. Of former smoking patients, only 28% had stopped smoking after transplantation. Patients younger than 55 years of age and females were more likely to quit than older or male patients. Smokers were significantly less likely to be transplanted compared to nonsmokers. Detection of smoking habits is typically dependent on patient self-reporting, seemingly a rather unreliable practice. In a cohort of 233 kidney transplant recipients, 45% were reported never to have smoked. In this group, serum cotinine serum levels were unrecordable.[54] Among the 55% with a lifetime history of smoking, cotinine level was diagnostic of current smoking in 32 (25%). However, only 66% of the current smokers admitted to the nephrologist that they had continued smoking and 34% claimed to be nonsmokers. The authors concluded that identification of current smokers among kidney transplant recipients should start with questioning about lifetime history of smoking and if positive, measurement of cotinine serum level.

Dyslipidemia

After transplantation, the prevalence of hypercholesterolemia is 60% and hypertriglyceridemia is 35%.[55] Most immunosuppressive drugs, with the exception of the antimetabolites, adversely impact dyslipidemia. Various reviews have described the differential effects of sirolimus, cyclosporine, and tacrolimus on dyslipidemia that range in severity from most to least, respectively.[3,4] Approximately 70% of CsA-treated kidney transplant patients have serum cholesterol levels higher than 200 mg/dl and 30% higher than 250 mg/dl.[56] In addition, low-density lipoprotein (LDL) oxidation is increased in patients treated with cyclosporine.[57,58] Oxidized LDL is thought to play a crucial role in the development of arteriosclerotic lesions, as it is toxic for endothelial cells and triggers endothelial dysfunction.[59] Kidney transplant recipients, and particularly those treated by CsA, have an increased incidence of endothelial dysfunction, which is revealed by impaired endothelium-dependent vasodilatation.[60,61]

Because cardiovascular disease is so prevalent in kidney transplant recipients, it is reasonable to consider the kidney transplantation state to be a "coronary heart disease risk equivalent" when applying guidelines.[62,63] This implies targeting plasma LDL cholesterol to less than 100mg/dl via a combination of therapeutic lifestyle changes and drug therapy. Changing immunotherapy may also impact dyslipidemia in a beneficial matter. For example, switching to tacrolimus from sirolimus or cyclosporine and withdrawing steroids may permit normalization of lipid levels without any other pharmacological intervention.

Statins are the lipid-lowering drugs of choice in transplant recipients. A recently published trial that investigated the use of fluvastatin in kidney transplant recipients (Assessment of Lescol in Kidney Transplantation [ALERT]) demonstrated efficacy in lowering cholesterol levels.[64] More importantly, cardiac deaths and nonfatal myocardial infarcts, although not overall mortality, were also significantly reduced after a mean of 6.7 years of follow-up. Of note, earlier reports of this study that failed to demonstrate use in reducing cardiovascular events should remind the reader that most statin trials reveal divergent outcomes only after 5 or more years of follow-up.

It should also be remembered that statin metabolism is at least partly inhibited by CI therapy that can lead to elevated blood and tissue concentrations and risk of adverse effects such as rhabdomyolysis. Consequently, PhRma indicates that statins be used at reduced doses in cyclosporine treated

transplant recipients. This interaction is further enhanced, if additional inhibitors of cytochrome P-450, such as diltiazem, are administered. Other measures that are often considered in order to minimize the risk of toxicity include the use of pravastatin or fluvastatin (which appear to have the least interaction with CIs), avoidance of other inhibitors of the cytochrome P-450 system, avoidance of fibrates, and periodic checking of plasma creatine kinase and liver function tests are also advisable.[65] Early reports that indicated that pravastatin may reduce the risk of rejection in kidney and heart transplant recipients are probably of less relevance in the current era of "modern" immunosuppression.[66,67] Rarely, nonstatin drugs are used to lower plasma lipids in transplant patients. Bile acid sequestrants, if used, should be taken separately from CI as they impair absorption of these drugs. Fibrates should be prescribed with extreme caution to patients on statins and CI.

New Onset Diabetes after Transplantation

The development of new onset diabetes after transplantation (NODAT) is a serious complication of transplantation that is associated with dyslipidemia, chronic allograft dysfunction, cardiovascular morbidity, and death.[68,69] The incidence of NODAT is definition dependent and ranges from 2% to 53%.[70,71] Risk factors include obesity, weight gain, hepatitis C, steroids, tacrolimus, and restoration of insulin metabolism by the kidney allograft.[72] For reasons that are unclear, autosomal dominant polycystic kidney disease (ADPKD) is also a risk factor for NODAT.[73] The causative pathophysiological mechanisms include a decrease in the number and binding affinity of insulin receptors, malabsorption of glucose in peripheral organs, and activation of the glucose/fatty acid pathway. Such mechanisms appear particularly important in those with significant posttransplantation weight gain.[74]

The introduction of CI therapy, particularly tacrolimus, increases the risk of NODAT.[75] Early studies indicated that up to 20% of tacrolimus-treated patients developed diabetes and required insulin, although the generally accepted number currently is about 7%.[3,4] Both in vitro and biopsy studies indicate that CI impair pancreatic β-cell function causing islet cell injury,[76] leading to diminished insulin synthesis or secretion, or both.[77–81] Tacrolimus has previously been shown to impair first phase (or early) insulin secretion,[82] while CsA has been shown to impair the second phase, (or later, sustained) insulin secretion.[83] The clinical significance of the latter observation is unclear.

Steroids primarily induce hyperglycemia by causing insulin resistance by increasing hepatic gluconeogenesis, inhibiting peripheral glucose uptake and also by impairing insulin secretion.[84,85] Reducing or withdrawing steroids has been shown to ameliorate hyperglycemia.[86,87]

The prognosis of NODAT is variable, although some studies indicate that up to one third of patients ultimately regain euglycemia off treatment.[88] This figure may be higher if such patients undergo steroid minimization or withdrawal along with a reduction or change in CI therapy.[89] However, most patients require a long-term approach to management that includes therapeutic lifestyle change, oral hypoglycemics or insulin, or both. Tight control of blood sugars has been shown to slow the progression of end-organ damage in diabetes; similar benefits are likely in kidney transplantation patients. It should be remembered that in spite of beneficial effects of tacrolimus on parameters such as HTN, GFR, and lipids, registry data indicate that there is no difference in patient or graft survival between those patients who receive cyclosporine and tacrolimus.[90] This observation is probably explained by the deleterious effect of tacrolimus-induced NODAT on long-term patient survival.

Metabolic Syndrome

The metabolic syndrome (MS) is known to be a risk for cardiovascular disease in the general population. In a study of more than 300 transplant recipients, 32% met criteria for MS at one year.[91] Predictive factors for MS included older age, male gender, pretransplantation high body mass index (BMI), and an increase in BMI after transplantation. Additionally, the cumulative incidence of adverse events was more than three times greater in patients with MS compared to others without MS. In another study, MS was present in 54% of transplant recipients.[92] In this cohort, there was a significant correlation between the various components of the MS and severity of coronary artery calcification (CAC). Median CAC scores were 0, 33, 98, and 262 for patients with one, two, three, and four or more positive components of the MS respectively. It has also been suggested that MS is related to inflammation as measured by CRP levels in transplant recipients.[93] The effect of a 12-month dietary regimen on the nutritional status and metabolic outcome of kidney transplant recipients in the first posttransplantation year was recently reported by Rike and colleagues.[94] Forty-six deceased-donor kidney transplant recipients were enrolled during the first posttransplant year and followed prospectively for a further 12 months. Compliance with dietary recommendations was related to gender (male better than female) and was associated with weight loss primarily due to a decrease in fat mass, with decrease in total cholesterol and glucose plasma levels and with a concomitant rise in serum albumin.

Obesity

The epidemic of obesity in the United States has not spared kidney transplant candidates. Obesity trends in transplant recipients tend to mimic the general population, 65% of who are now defined as overweight (BMI greater than 25 kg/m^2). There are several factors that contribute to weight gain, including steroid use, removal of dietary restrictions after transplantation and physical inactivity. Obesity is an established risk factor for atherosclerotic heart disease and increases the risk for diabetes, dyslipidemia and hypertension.[95] Obesity is also known to be associated with depression after transplantation.[96] Bosma and colleagues described an association between obesity and iothalamate determined glomerular hyperfiltration in 838 kidney transplants.[97] With higher BMI, GFR, and filtration fraction (FF) increased significantly. Multivariate analysis supported the impact of BMI on GFR and determined that this association was not explained by diabetes mellitus. On Cox-regression analysis, lower GFR and higher FF were

independent determinants of graft loss and patient mortality. It is now known that the likelihood of receiving a transplant decreases with increasing degree of obesity as compared to nonobese patients.[98] Similarly, the likelihood of being bypassed when an organ became available increases in a graded manner with category of obesity. The defining questions about obesity and transplantation are whether the former impacts outcomes and whether weight loss prior to transplantation is a mitigating factor. In a study of 5700 patients, obesity was associated with poor graft and patient survival only in univariate and not in multivariate analyses.[99] Perhaps surprisingly, underweight patients had greater late death-censored graft loss, mainly due to chronic allograft nephropathy. However, obesity was associated with greater odds risk for DGF and 6-month risk of acute rejection. Management of obesity includes lifestyle changes, dietary modifications, and in some cases gastric bypass or banding for which the published experiences in transplant recipients is limited.[100,101]

Posttransplantation Anemia

Posttransplantation anemia is present in more than 50% of kidney recipients at some stage after surgery.[102,103] Immediately posttransplantation, anemia is a consequence of postoperative blood loss, the use of myelosuppressive immunosuppressive medications such as antimetabolites, sirolimus and antithymocyte globulins, inflammation, and defective erythropoietin production by the transplanted kidney.[104,105] Furthermore, anemia can persist months after transplantation due to several factors including antiviral therapy, allograft dysfunction, or infection.[106] Table 39-1 summarizes the major causes of anemia in kidney transplant recipients and their mechanisms.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) exacerbate or induce anemia in the transplant patient although for reasons that are incompletely understood.[107] In the TRESAM study, data from 4263 patients from 72 transplant centers in Europe was collected 6 months to 5 years posttransplantation.[108] The mean hemoglobin levels before transplantation were significantly higher in the more recently transplanted recipients. At enrollment, 39% of patients were found to be anemic. Of the 8.5% of patients who were considered severely anemic, only 18% were treated with recombinant human erythropoietin (rHuEpo). Anemia was associated with impaired kidney function and use of azathioprine, ACE inhibitors, and ARB therapy.

Recombinant human erythropoietin is often administered to patients with CKD and more frequently to patients on dialysis. The use of rHuEpo after kidney transplantation remains to be defined. Van Biesen and associates reported the results of a trial in which patients were randomized to either receive rHuEpo three times a week immediately after transplantation or not. The time to reach a hemoglobin level greater than 12.5 g/dl was 66 days in the rHuEpo group compared to 57 days in the control group. The authors concluded that while the administration of rHuEpo reduced the duration of anemia, this effect was marginal, and the doses needed were high.[104] There was no difference in harder endpoints such as length of stay or patient or graft survival between the groups.

TABLE 39-1 Causes of Anemia in Kidney Transplant Recipients

CAUSE	MEDIATED BY	ULTIMATE EFFECT
Allograft dysfunction Hyperparathyroidism Inflammation	Erythropoietin deficiency	Decreased bone marrow production of RBCs
Azathioprine MMF/MPA SRL TMP-SMX(val) ganciclovir Antithymocyte globulins	Myelosuppression	Decreased bone marrow production of RBCs
ACE inhibitors ARB	Impaired production of, or resistance to, erythropoietin	Decreased bone marrow production of RBCs
Iron deficiency	Impaired synthesis of hemoglobin	Decreased bone marrow production of RBCs
Minor ABO incompatibility	Donor antibodies	RBC hemolysis
Posttransplantation hemolytic uremic syndrome	Multiple factors, including genetic defects, viral infection, calcineurin inhibitors, antiphospholipid antibodies	RBC hemolysis
Gastrointestinal or other bleeding	Red blood cells	RBC losses exceed production

This table shows only the more common causes of anemia posttransplantation. Frequently, more than one is present in the individual recipient.
ACE, angiotensin converting enzyme; *ARB*, angiotensin receptor blockers; *MMF/MPA*, mycophenolic mofetil/mycophenolic acid; *RBC*, red blood cell; *SRL*, sirolimus; *TMP-SMX*, trimethoprim-sulfamethoxazole.

Peripheral and Cerebrovascular Disease

Dialyzed and kidney-transplanted patients have a higher rate of peripheral vascular complications than the general population.[1,109,110] Although transplantation is associated with significantly better survival than dialysis,[111] kidney transplant recipients remain at high risk of vascular complications.[112–114] This risk can be enhanced by immunosuppressive drugs.[115] Kasiske and associates[55] reported a 15% prevalence of peripheral vascular disease at 15 years posttransplantation. Sung and associates[116] retrospectively studied 664 adult recipients and found a cumulative 5- and 10-year incidence of 4% and 6%, respectively; the presence of peripheral vascular disease was independently associated with poorer recipient survival. There is also some evidence from registry data that peripheral vascular disease is a risk factor for poor graft outcomes.[117] It therefore seems reasonable to aggressively treat patients with this condition with measures, such as aspirin, statins, smoking cessation, and revascularization where appropriate.

Evaluation of Atherosclerotic Cardiovascular Disease before Transplantation

Given the high incidence of preexisting ASCVD in the ESRD population, screening for such disease remains an important part of the transplant evaluation prior to surgery.

Such investigations generally include electrocardiography, echocardiography, provocative stress testing, and cardiac catheterization when needed as the standard of care. Nevertheless, the efficacy of such an approach has been debated as patients awaiting transplantation have high mortality rates despite careful preselection. Hage and coworkers examined mortality outcomes in 3700 patients with ESRD referred to a single center for transplantation.[118] The mean age of the cohort was 48 years, and 42% were female. Stress myocardial perfusion imaging was performed in 60% and coronary angiography in 7%. Over a period of 30 months, 17% of the cohort died. Interestingly, neither the presence nor severity of coronary disease as defined by angiography predicted survival. Coronary revascularization did not impact survival either except in patients with three-vessel disease. The best predictor of death was left ventricular ejection fraction (LVEF), measured by gated myocardial perfusion imaging, with 2.7% mortality increase for each 1% ejection fraction decrease. Conversely, Bergeron and colleagues studied the outcome of 485 patients with CKD who had undergone dobutamine stress echocardiography (DSE) as part of an evaluation for transplantation who were followed for more than 2 years.[119] Almost 40% of the patients died during the follow-up period. Patients with more extensive ischemia had inferior outcomes compared to those with lesser degrees of ischemia and also those with a normal stress testing. By multivariate analyses, the percentage of ischemic segments on DSE was an independent predictor of all-cause mortality. Vanrenterghem reported the prognostic power of stress myocardial perfusion imaging (MPI) in 150 patients with ESRD being evaluated for renal transplantation with known coronary anatomy based on angiography.[12] An abnormal MPI result was present in 85% of patients, 30% had left ventricular ejection fraction of less than 40%, and 40% had multivessel coronary artery disease using angiography. After 3 years, 35% patients had died. Low ejection fraction, left ventricular dilatation, and diabetes mellitus were all associated with higher mortality. In a multivariate model, abnormal MPI results (low LVEF or abnormal perfusion) and diabetes alone were independent predictors of death, whereas number of narrowed arteries using coronary angiography was not. Thus, MPI was a strong predictor of all-cause mortality in patients with ESRD. In truth, as a consequence of the observation that cardiovascular disease is the major cause of mortality in the peritransplant period, most transplant programs insist on echocardiography and provocative stress testing as a prerequisite for listing.

Hickson reported a different approach to cardiac risk stratification using cardiac troponin T (cTnT) from a cohort of 644 patients of whom 61% had elevated levels.[120] Higher levels related to diabetes, longer time on dialysis, history of ASCVD, and low serum albumin. High cTnT levels related to specific cardiac anomalies including left ventricular hypertrophy, wall motion abnormalities, and stress-inducible ischemia. Importantly, increasing cTnT levels were associated with reduced patient survival independent of serum albumin. In this study, the results of the stress testing or coronary angiography, or both, did not impact survival. However, high cTnT identified patients with abnormal echo findings and poor survival. Waitlisted patients with normal cTnT had excellent survival irrespective of other factors.

It has been suggested that normalization of GFR may alter *coronary artery calcification* after transplantation. Schankel and colleagues studied this issue by performing electron-beam computed tomography (CT) in 82 subjects at time of transplantation and at least 1 year later.[121] Curiously, calcification scores actually increased over time. In multivariate analysis, diastolic blood pressure, Caucasian race, GFR, months posttransplant, BMI, and baseline CAC score were independent predictors of annualized rate of CAC change. Consequently, it seems that reasons other then arterial calcification are responsible for the favorable outcome associated transplantation from a cardiovascular perspective.

Table 39-2 summarizes the adverse effects associated with the various immunosuppressant medications currently in clinical use.

MALIGNANCY AFTER KIDNEY TRANSPLANTATION

Improvements in patient and graft survival rates in renal transplantation remain overshadowed by the long-term risk of malignancy. With the exception of skin cancer, recipients of kidney transplants are about three to four times more likely to develop neoplastic disorders than the general population.[122]

TABLE 39-2 Adverse Effects of Immunotherapy

BIOLOGICAL EFFECT	CsA	Tac	SRL	Pred	MMF/MPA
Hypertension	++	+	–	++	–
Nephrotoxicity	+++	++	+	++	–
Dyslipidemia	++	+	++++	++	–
Hyperglycemia	+	++	–	++	–
Hyperkalemia	++	+++	–	–	–
GI side effects	–	+	+	–	++
Tremor	+	++	–	–	–
Malignancy	+	+	Less	–	?
Osteoporosis	+	+	–	++	–
Hirsutism	+	–	–	–	–
Gingival hypertrophy	–	+	–	–	–
Alopecia	–	+	–	–	–

CsA, cyclosporine; *GI*, gastrointestinal; *MMF/MPA*, mycophenolic mofetil/mycophenolic acid; *Pred*, prednisone; *SRL*, sirolimus; *Tac*, tacrolimus.

In general, there are three types of malignancy that have features specific to the transplanted population:

- Posttransplant lymphoproliferative disease (PTLD)
- Nonmelanoma skin cancer
- Kidney cell carcinoma arising from (atrophic) native kidneys

The relationship between the nature and intensity of immunotherapy and subsequent malignancy is well-defined and has been described in prior reviews.[4,123] It remains clear that the incidence of all types of cancer is higher for allograft recipients than the general population. In a recent study of more than 2000 kidney transplant recipients with 20 or more years of graft function, more than 40% had developed skin cancer and more than 10% had developed cancer at other sites.[124] Importantly, cancer was the second most common cause of death after cardiovascular disease. In another study, the cumulative incidence of cancer after 25 years was 49% for all tumors.[125] The most frequent tumors observed were non-melanoma skin cancer (21%), kidney cancer (12%), and cancers of the pharynx, larynx, or oral cavity (8%). The increase in cancer risk was 4.3-fold. Webster and associates reported standardized ratios of cancer in transplant recipients compared to the general population using the Australia and New Zealand Dialysis and Transplant Registry data.[126] Over a 20-year period, 11% of 15,000 recipients developed cancer. The risk of cancer was found to be inversely related to age, and women aged 25 to 29 years had rates equivalent to women aged 55 to 59 years from the general population. Within the transplanted population, the cancer risk was affected by age differently for each sex and was elevated by prior malignancy but reduced by diabetes. The authors concluded that cancer rates in kidney recipients are similar to people in the general population that are 20 to 30 years older, but the absolute risk differs across patient groups.

The increase in cancer risk after transplantation is thought to result from the complex interplay of numerous factors that include cumulative exposure to immunosuppression that leads to disruption of both antitumor and antiviral immune-surveillance.[126,127] Additionally, some drugs may promote carcinogenesis by mechanisms independent of their immunosuppressive effects. Viral infections (particularly herpes, hepatitis, and papilloma viruses) are clearly linked to some malignancies, and chronic antigen stimulation from the transplanted organ, repeated infections, and transfusions of blood products have also been implicated.

Impact of Immunosuppression

It has been suggested that the use of antilymphocyte antibody therapy and tacrolimus increase the risk of posttransplant lymphoproliferative disease.[128,129] Hardinger and associates recently reported the 10-year follow-up of a randomized trial of Thymoglobulin (Genzyme, Cambridge, Mass) or Atgam (Pharmacia-Upjohn, New York) induction.[130] Event-free survival was significantly higher with Thymoglobulin compared with Atgam (48% vs. 29%). At 10 years, patient and graft survival rates were similar, whereas acute rejection remained lower (11% vs. 42%) in the Thymoglobulin group. The incidence of all types of cancer was numerically although not significantly lower with Thymoglobulin compared to Atgam (8% vs. 21%). There were no posttransplant lymphoproliferative disorder cases in the Thymoglobulin group and there were two cases in the Atgam group. Kidney function and measures of quality of life were found to be higher in the Thymoglobulin compared to Atgam group. Wimmer and colleagues reported that the use of IL-2 receptor antagonists as induction therapy significantly reduced the cancer risk of transplant recipients.[125] With the exception of mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus), tumor risk between immunosuppressive drugs typically used for maintenance immunosuppression was not significantly different. However, mTOR inhibitor-based immunosuppressive protocols showed a clear tendency for lower malignancy rates.[131,132] Acknowledging the potential anticancer actions of the mTOR inhibitors demonstrated in clinical studies, de Fijter analyzed the effect of conversion from CIs in 53 renal transplant recipients developing nonmelanoma skin cancer after transplantation.[133] Remission was observed in 37 patients, and therapy was generally well-tolerated with minimal adverse events reported. Fifteen patients developed new lesions following conversion. Drug levels did not seem to affect the outcomes of conversion. Interestingly, the use of sirolimus has recently been shown to reduce levels of prostate specific antigen by 50% in with patients without prostate cancer.[134] Why this occurs is unknown.

Reports continue to accumulate indicating that Kaposi sarcoma (KS) after transplantation is exquisitely sensitive to conversion from CI to mTOR inhibitor therapy. As an example, Campistol and coworkers reported that conversion to either everolimus and sirolimus led to regression of KS lesions in 11 out of 12 patients.[135] Conversion was generally well-tolerated, stable kidney function was maintained in most patients and there was no rejection. Similarly, Di Paolo and colleagues studied mTOR-signaling pathways in 10 renal transplant patients with KS who successfully responded to mTOR inhibitor conversion therapy.[136] Patients with KS showed markedly increased basal P70 (S6K) activation and depressed phosphorylation of AKT. Long-term treatment with sirolimus was associated with marked inhibition of phosphorylation of both AKT and P70 (S6K), in parallel with regression of the dermal neoplasm.

In spite of the benefits described above, mTOR inhibitors have failed to gain traction because of the high incidence of symptomatic adverse effects that include increased risk of infection, wound problems, edema, mouth ulcers, and proteinuria that are seen in up to 25% of patients and lead to conversion to alternate immunotherapy. Nevertheless, for those recipients suffering from cancer after transplantation, such agents may be useful. The reader's attention is directed to a report prepared by an international group pertaining to the use of "proliferation signal inhibitors" (referred to as mTOR inhibitors above), everolimus and sirolimus and their antioncogenic effects.[128]

Posttransplantation Lymphoproliferative Disease

Transplant recipients are at the greatest risk of developing lymphoproliferative diseases (PTLD) within the first year after transplantation. Most cases of PTLD are induced by

Epstein-Barr virus (EBV) infection causing uncontrolled proliferation of B-cells. The incidence is higher in EBV seronegative children who receive seropositive grafts from adult donors. Heart-lung transplants showed the highest relative risk among different types of organ transplants.[3] The use of tacrolimus and induction or rescue therapy with OKT3 or antithymocyte globulin (ATG) is known to increase the risk of PTLD.

While EBV infection is known to be associated with the development of PTLD, the prognosis of such transplant recipients has been less clear. Smith and colleagues described the outcomes of pediatric kidney transplant recipients with PCR-defined EBV infection after ganciclovir prophylaxis.[137] Primary infection developed in 46 patients of whom 50% were asymptomatic, 26% were symptomatic and 24% developed PTLD. Adolescents were more likely to develop PTLD than younger transplant recipients. Among the 11 cases of PTLD, there were 2 deaths and 2 graft failures all in adolescent recipients. Suzuki and colleagues performed a prospected study of 32 tacrolimus-treated kidney transplant recipients that included EBV serology and PCR testing.[138] Seroconversion occurred in five of six patients approximately 22 weeks after transplantation. The viral load was significantly higher in seronegative compared to the seropositive patients.

The diagnosis of PTLD is generally suggested by clinical symptoms (organ involvement or fever, or both) and imaging study results. The clinical symptoms that patients complain of are extremely variable and depend on the site and stage of PTLD. Traditionally, CT scanning with oral and intravenous contrast has been the test of choice for defining the presence and extent of PTLD. It has been suggested that fluorodeoxyglucose-positron emission tomography (FDG-PET) inline with CT scanning may be a superior methodology.[139] In a report of four transplant recipients with histologically confirmed PTLD, scans at diagnosis showed increased FDG uptake in all examined PTLD lesions, and the disease was upstaged on the basis of FDG-PET/CT scan results over conventional CT scanning in one patient. Furthermore, PET/CT scans no longer demonstrated FDG uptake in the original PTLD lesions in all patients at the end of treatment.

Treatment of Posttransplant Lymphoproliferative Disease

The current approach to the treatment of PTLD involves a number of therapeutic options that include:

- Reduction of basal immunosuppression
- Antiviral treatment in the case of EBV-positive B-cell lymphoma
- Rituximab in the case of CD20-positive lymphomas
- Cyclophosphamide, hydroxydaunomycin/doxorubicin, Oncovin, prednisone (CHOP) chemotherapy alone or in combination with rituximab for diffuse lymphoma or incomplete response to previous treatment

Swinnen and associates reported the results of a prospective, multicenter study that examined the efficacy of a PTLD treatment algorithm that started with a defined course of reduced immunotherapy and escalated to interferon-α2b, and finally to chemotherapy.[140] Intravenous acyclovir was given to all patients. The CI was reduced by 50% for 2 weeks and then by another 50% unless the patient was in complete remission. Sixteen patients with biopsy-proven PTLD were eligible to participate in the study of who 13 had received heart transplants and three kidney transplants. Reduced immunotherapy resulted in only 1 of 16 partial responses and no complete remissions. Progressive disease developed in half and 40% experienced rejection. Only 1 of 13 patients achieved durable remission with interferon. Five of seven patients who received chemotherapy achieved remission. The applicability of such a study to kidney transplantation remains uncertain, as most patients in that study were heart transplant recipients. The authors concluded, "A strong case can be made for adding rituximab to RI [reduction in immunosuppressives] as initial therapy." Trappe and colleagues performed a retrospective analysis to determine the efficacy and safety of salvage therapy in recipients of solid organ transplants with progression of PTLD after rituximab first-line therapy.[141] Eleven patients who had received reduced immunotherapy and single-agent rituximab were analyzed. Of these, 10 had received CHOP. This cohort seems to be have been quite different from usual PTLD cohort in that most of these patients had late disease (median onset of disease 145 months posttransplant) and had monomorphic histology, and only 36% were associated with EBV. CHOP therapy achieved complete remission in 50% of patients at 44 months posttreatment and partial remission of 20% of patients. The median overall survival was 46.5 months.

ELECTROLYTE DISORDERS

Electrolyte disorders are common after kidney transplant. Hyperkalemia can be induced by poor graft function CIs, particularly tacrolimus; and other drugs such as ACE inhibitors, ARBs, or beta blockers. Treatment is similar to that of hyperkalemia in CKD: reduction in potassium intake, adjustment in medications, and administration of loop diuretics. Kayexalate should be avoided immediately post-transplantation because of a rare but potentially catastrophic complication of colonic perforation.[142,143] Therefore, refractory hyperkalemia complicating delayed graft function is best treated with dialysis.

Hypophosphatemia is almost universal after kidney transplantation once good graft function is achieved. It generally lasts for a few months and is often of sufficient severity to warrant oral and occasionally parenteral phosphorus supplementation. It was generally thought to be to persistent hyperparathyroidism. However, hypophosphatemia can occur despite low parathyroid hormone (PTH) levels and can persist after high PTH levels normalize. A novel growth factor, fibroblast growth factor-23 (FGF-23) that induces phosphaturia, inhibits calcitriol synthesis, and accumulates in CKD has recently been implicated as a dominant cause of hypophosphatemia after transplantation.[144–146] Bhan and associates studied 27 living donor transplant recipients of whom 85% developed hypophosphatemia.[145] FGF-23 levels dropped by more than 50% within the first week after transplantation, although they still remained higher than normal. Furthermore, FGF-23 was independently associated with serum phosphate, urinary excretion of phosphate, and calcitriol levels; PTH was not independently associated with any of these parameters. Similarly, Evenepoel and associates

studied 41 patients before and 3 months after transplantation.[144] In this cohort, FGF-23, but none of the other mineral metabolism indices, was an independent predictor of the phosphate nadir in the early posttransplant period.

MUSCULOSKELETAL COMPLICATIONS OF TRANSPLANTATION

Immunotherapy and secondary hyperparathyroidism are considered among the more important pathogenetic factors leading to post kidney transplantation bone disease. Other implicated causes of include preexisting uremic osteodystrophy (hyperparathyroidism, aluminum osteomalacia, ß2 microglobulin-associated amyloidosis, and diabetic osteopathy), poor kidney function, and ongoing secondary hyperparathyroidism, hyperphosphaturia, and pathogenic vitamin D alleles. The main syndromes are bone loss with a consequent fracture rate of 3% per year, osteonecrosis of the hip, and bone pain.[147] The bone of a typical kidney transplant patient will pass through four phases:

1. The development of uremic osteodystrophy before kidney transplantation
2. Exacerbation immediately after kidney transplantation caused by high-dose immunosuppressive therapy and continuing homeostatic disturbances
3. A phase of stabilization secondary to immunosuppressive dose reduction and reestablishment of normal homeostasis
4. The return of uremic osteodystrophy caused by failing graft function[147]

Osteopenia and Osteoporosis Posttransplantation

Bone loss is particularly pronounced during the first year after transplantation, leads to about a 9% reduction in bone mineral density, and may persist for several years, even in patients with normal kidney function. Recent studies indicate that osteoblast apoptosis and impaired osteo blastogenesis play important roles in the pathogenesis of glucocorticoid-induced osteoporosis. In a study of 20 patients with a mean age of 36 years who were subjected to bone biopsy after kidney transplantation, the main alterations in posttransplant biopsies were a decrease in osteoid and osteoblast surfaces, adjusted bone formation rate, and prolonged mineralization lag time.[148] In contrast with pretransplant biopsies, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells in the proximity of osteoid seams or in the medullary space were observed indicating that impaired osteo blastogenesis and early osteoblast apoptosis may play important roles in the pathogenesis of posttransplant osteoporosis.

While steroids have typically been implicated as the dominant cause of osteoporosis posttransplantation, animal studies have previously indicated that cyclosporine therapy may be an inducer of bone disease even in the absence of corticosteroids.[149] A recent study compared bone densitometry and histomorphometry in patients receiving cyclosporine monotherapy versus those receiving azathioprine and steroid therapy.[150] Bone mineral density was low in both immunosuppressive regimens, and there were no significant differences between the groups. Histopathological analysis indicated that mixed uremic bone disease was present in 42%, adynamic bone in 29%, and hyperparathyroid disease in 17%. Normal bone was seen in only 12%. Patients showed a slight increase in osteoclast number and function, decreased osteoblast number and function, and retardation of dynamic parameters. No differences in histopathological diagnosis or histomorphometrical findings were observed between the immunosuppressive therapy groups. The authors concluded that both cyclosporine and steroid therapies were associated with slight osteoclast stimulation and osteoblast suppression and marked retardation of mineral apposition and bone formation rates. Both drugs also were associated with reduced bone density.

Treatment of Posttransplant Osteopenia and Osteoporosis

One of the problems with the clinical trials in preventing bone disease post transplantation is the focus on secondary endpoints such as biochemical changes, alterations in bone density, or occasionally histology as against a primary endpoint such as fracture risk. One such study examined intravenous pamidronate as compared to vitamin D and calcium.[151] Patients on pamidronate demonstrated preservation of bone mass at 6 and 12 months as measured by bone densitometry, whereas control patients lost bone mass. Of some concern, all of the pamidronate treated patients had histological evidence of adynamic bone disease at 6 months, whereas 50% of control patients continued to have or developed decreased bone turnover. There was no reported difference in fracture risk.

A metaanalysis of 23 clinical trials in posttransplant bone disease totaling 1209 patients was recently reported.[152] Significant improvements in spinal and femoral bone mineral density were reported with the use of bisphosphonates and vitamin D analogues. Calcitonin improved spinal, though not femoral, neck bone mineral density. The incidence of reported toxicity was low. No trial found a reduction in fracture risk. Another recent trial examined the use of two doses of zoledronate at 2 and 12 weeks posttransplantation in a cohort of 20 patients.[153] Although zoledronate was associated with an early improvement in bone density, this benefit was not sustained at 3 years. Increasingly, investigators are examining the impact of bone intervention strategies in children who have been transplanted. For example, one study examined 30 children or adolescents with low-bone mineral density at 48 months posttransplantation.[154] The patients were randomized to either take daily alfacalcidol 0.25 mcg or placebo. After 12 months of treatment, bone density was significantly worse in the placebo group compared to a significant improvement in the treatment group. Enthusiasm for the widespread use of bisphosphonates in transplant patients most recently has been tempered by reports of significant adverse effects. For example, reports of collapsing glomerulopathy and other glomerular epithelial cell disorders are accumulating with the use of high dose pamidronate.[155] Most recently, hundreds of cases of jaw osteonecrosis have been reported from around the world related to bisphosphonate therapy.[156] Admittedly, most such cases have occurred to patients receiving high dose parenteral

therapy in the setting of hematological malignancy frequently precipitated or realized at the time of dental extraction.

Another reported approach to the management of osteoporosis after transplantation is the avoidance or minimization of steroids. In a study of 364 transplant recipients, ter Meulen and coworkers randomized patients to steroid-free therapy or prednisone (0.3 mg/kg per day tapered to 0 mg at week 16) after transplantation.[157] All patients received tacrolimus, mycophenolate mofetil, daclizumab, and, during the first 3 days, 100 mg prednisolone intravenously. Lumbar spine bone density decreased slightly in both groups during the first 3 months after in the following months lumbar bone mineral density (BMD) recovered in both groups. No difference between the groups was found at either 3 months or 12 months after transplantation. The authors concluded that moderate dose steroid has little impact on bone density within the first post transplant year.

Osteonecrosis post kidney transplantation has been largely attributed to the use of steroids. However, other risk factors such as microvascular thrombosis, hyperlipidemia, and alternate immunotherapies have been described. The incidence of hospitalized osteonecrosis reported to the United States Renal Data System (USRDS) is 7.1 episodes/1000 person-years.[158] A single-center radiological survey of 49 patients revealed an osteonecrosis incidence of 4% by plain radiograph and magnetic resonance imaging (MRI).[159] In a recent report based on analysis of the USRDS, 3.5% of patients who received the combination of sirolimus and cyclosporine developed osteonecrosis, compared to 1.4% of patients who received the combination of sirolimus and tacrolimus.[159] In a multivariate analysis, the use of cyclosporine compared to tacrolimus was independently associated with an increased risk of osteonecrosis.

Matas and associates recently reported data from a 5-year trial of prednisone-free maintenance immunosuppression.[160] In this study, almost 600 kidney transplant recipients were treated with a protocol that involved discontinuation of their prednisone on postoperative day 6. At 5 years, the actuarial patient survival was 91%; graft survival, 84%; death-censored graft survival, 92%; acute rejection-free graft survival, 84%; and chronic rejection-free graft survival, 87%. In all, 86% of kidney recipients with functioning grafts remain prednisone-free. As compared to historical controls, recipients on prednisone-free maintenance immunosuppression had a significantly lower rate of avascular necrosis, and fractures.

Osteoarticular Pain Posttransplantation

Osteoarticular pain post transplantation occurs in up to 10% of patients soon after transplantation and typically effects the lower extremities.[161–163] This complication has been described in patients taking both cyclosporine and tacrolimus. The clinical evaluation is unremarkable and the described radiological features include:

- Epiphyseal patchy osteoporosis at radiograph
- Increased focal or diffuse uptake of the tracer at bone scintigraphy
- Areas of low-signal intensity at T1-weighted images on MRI

The MRI abnormalities are generally believed to be consistent with areas of medullary edema, although some authors suggest that the syndrome may be related to "microfractures" or impaction and may be related to subclinical trauma.[162] Clinical recovery is the rule and usually occurs within several weeks. It has been suggested that patients refrain from excessive physical activity shortly after transplantation order to minimize risk of locomotor injury.

Tendonitis

Achilles tendonitis with ruptures was initially described in patients taking high dose quinolone antibiotics more than a decade ago. More recently, a case control study reported a four fold overall increased risk for tendonitis and ruptures in patients taking steroids.[164] This study identified a six fold increase in odds risk (OR) in patients aged 60 to 79 years and a 20-fold increase in odds risk in patients aged 80 years or older. In persons aged 60 years and older, the OR was 28 for current exposure to ofloxacin. Approximately 2% to 6% of all Achilles tendon ruptures in people older than 60 years can be attributed to quinolones. An ultrastructural study of tenocytes from rats exposed to quinolones exhibited degenerative changes such as multiple vacuoles and large vesicles in the cytoplasm that resulted from swelling and dilatation of cell organelles (mitochondria, endoplasmic reticulum).[165] The nucleus became dense and the chromatin had clumped to form rough plaques. The cells detached from the extracellular matrix. Other important findings were a general decrease of the fibril diameter and an increase in the distance between the collagenous fibrils. Consequently, high dose quinolones should be used with caution in older patients on steroids.

NEUROPSYCHIATRIC COMPLICATIONS OF TRANSPLANTATION

The development of ESRD combined with the realization that life may no longer be possible without medical intervention may lead to anxiety, depression, non-adherence with diet or medications, sexual dysfunction, and suicide in the transplantation patient.[166] Immunotherapy has also been implicated in causing psychiatric disturbances that may include euphoria, delirium, generalized anxiety disorder, and occasionally, hallucinations.[167] Such disorders often require intervention with psychopharmacological agents. However, psychotropic drug administration may be hazardous because of pharmacokinetic interactions with immunosuppressive drugs.[168]

Depression

ESRD and transplantation are associated with depression, which impacts adversely upon compliance and may be associated with decreased longevity.[169,170] In the kidney transplant population, depression occurs early after transplantation and is associated with both acute and chronic rejection.[169] Depression is also common in recipients of other organ transplants. Among heart transplant patients, for example, the incidence of depression was as high as 34% beyond the first posttransplant year.[171] Similarly, 43% of patients with end stage liver

disease presented at least one psychiatric diagnosis. Child-Pugh score and previous psychiatric diagnoses were independent significant predictors of depressive disorders.[172] The specific factors that increase a heart transplant recipient's risk for depression and anxiety-related disorders include the following:

- Pretransplant psychiatric history
- Poor social support
- The use of avoidance coping strategies for managing health problems
- Low self-esteem

Other factors that may lead to depression include the disfiguring effects of immunosuppressive medication, such as high-dose corticosteroid therapy, and antihypertensive treatment with beta blockers.

Suicide

In one study, the crude suicide rate in kidney transplant recipients from 1995 to 2001 was 24 per 100,000 patient-years, a finding that was 84% higher than the general population.[166] In multivariate models, age greater than 75 years, male gender, white or Asian race, geographic region, alcohol or drug dependence, and recent hospitalization with mental illness were significant independent predictors of death as a result of suicide.

Nonadherence

Nonadherence (or noncompliance) with diet and medication is a major risk factor for rejection and is responsible for up to 25% of deaths after the initial recovery period.[169] In one study, the risk of acute graft rejection was 4.2 times greater among recipients who were noncompliant with medications.[173] The numerous factors implicated include psychiatric disturbances, adverse effects of medications, lack of knowledge concerning the need for medications, and financial concerns. This problem is particularly prevalent in adolescents and young adults. An overview of the literature reported that certain patient characteristics were closely linked to noncompliance among solid organ transplant recipients:[169]

- Younger and older age, and nonmarried
- Anxious and individuals prone to denial, and those with severe personality disorders or who are mentally retarded
- History of substance abuse

Additional factors underlying compliance include the particular transplant center and dosing frequencies of immunosuppressive medications, with higher dosing frequencies resulting in decreased adherence.

Psychopharmacology

Previous therapeutic options for depression were hampered by the adverse effects associated with traditional agents. By comparison, newer antidepressant medications are more effective and safer in both the general population and medically ill patients. This diverse group of compounds possesses distinct pharmacokinetic properties that are unrelated to either the tricyclic/tetracyclic antidepressants or the monoamine oxidase inhibitors. Such newer agents include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, trazodone, and fluvoxamine. Agents with serotonin reuptake activity that also prevent the uptake of other neurotransmitters (such as norepinephrine and dopamine) include nefazodone, bupropion, and venlafaxine.

A problem associated with the use of these agents may be drug interactions resulting in elevated cyclosporine levels due to alterations in the cytochrome CYP3A4 isoenzyme system. Among the newer antidepressant medications, fluvoxamine and nefazodone have the strongest inhibitory action on the CYP3A4 isoenzyme. In fact, we have previously reported interactions between cyclosporine and nefazodone or fluvoxamine that led to severe cyclosporine toxicity, allograft dysfunction and uncontrolled hypertension.[168] The corollary of such observations is that agents with minimal inhibitory effects on the CYP3A4 isoenzyme, such as paroxetine and sertraline, would not be expected to cause a pharmacokinetic interaction. Although fluoxetine has moderate inhibitory potency, it has not been implicated in causing such interactions. Information is lacking for trazodone, venlafaxine, and bupropion. Caution dictates that levels of affected drugs should be carefully monitored in any transplant patient who requires treatment for major affective disorders. Appropriate dosage adjustments should be performed as necessary to circumvent toxicity. For patients who require antidepressant medications, fluoxetine or bupropion are often used as first-line therapy since these agents have not been shown to have significant interactions with CIs.

Psychotherapy has also been studied in a cohort of approximately 80 recipients of primary deceased donor kidney transplants.[170] In this report, patients were randomized to receive either group therapy or individual psychotherapy without psychopharmacological intervention. Standardized depression scores improved in both groups, although patients who received individualized therapy had the greatest improvement in the depression score.

Neurological Complications

Tremors after transplantation are extremely common and are generally related to CI therapy. Cyclosporine has long been known to activate the sympathetic nervous system and increase circulating catechol levels. It is now understood that tacrolimus is an even greater offender in this regard.[38] Most often, such tremors are related to the higher levels that are required early posttransplantation in order to prevent allograft rejection. In general terms, tremors abate over time as the levels are allowed to run at a lower range.[174] A new onset tremor in a transplant recipient may be a clue to CI toxicity and should prompt a measurement of the drug level. Sirolimus and the antimetabolite immunosuppressive agents are not generally associated with this adverse event.

VISUAL DISTURBANCES AFTER TRANSPLANTATION

Ocular complications after transplantation are frequently encountered and range in severity from blurred vision from poorly controlled hyperglycemia to sight-threatening steroid-induced retinopathy. Cataracts develop in approximately

40% of transplant patients and lead to surgery in many of those afflicted.[175] Risk factors include diabetes mellitus, older age, and the use of corticosteroids. Diabetic retinopathy is often "burned out" by the time a diabetic comes to transplantation. However, for type I diabetics undergoing pancreas transplantation, active retinopathy may regress. Ocular infections consequent on immunotherapy such as CMV or toxoplasmosis are, fortunately, rare in the organ transplant population. As visual disturbances after solid organ transplantation may be sight threatening, any new symptoms are most appropriately evaluated by ophthalmology. Routine ophthalmological examinations are currently recommended for high-risk patients on an annual basis.

SUMMARY AND CONCLUSION

Although the introduction of more potent immunosuppressive agents has reduced the rates of acute rejection and early graft loss, late graft loss, and premature death continue to limit the long-term success of transplantation. Morbidity from posttransplant diabetes, malignancy, and bone disease is substantial. More attention is therefore being paid toward preventing and treating these medical complications of transplantation. In many ways, kidney transplant recipients need to be managed similarly to those with CKD. More effective intervention at the predialysis or dialysis stage also is needed to reduce the burden of morbidity in transplant patients. It is also of vital importance that nephrologists refer patients for transplant evaluation prior to beginning dialysis since patients can be listed for a kidney transplant once their GFR is less than 20 ml/min, and it is well-known that mortality decreases the earlier a patient is transplanted. Finally, reduction in long-term immunosuppression should be strongly considered in all patients.

A full list of references are available at www.expertconsult.com.

Chapter 40

RECURRENT AND DE NOVO RENAL DISEASES AFTER KIDNEY TRANSPLANTATION

Denise M. Sadlier, M.B., Ph.D., F.R.C.P.I., and
Yvonne M. O'Meara, M.D., F.R.C.P.I.

Recurrence of original disease following kidney transplantation affects between 10% and 20% of patients in most series, and accounts for up to 8% of graft failures at 10 years post-transplant.[1–5] Wide variation exists in the reported rates of recurrence of different diseases and the ensuing rates of graft loss (Tables 40-1 and 40-2). Accurate estimation of the incidence of recurrence is difficult for a number of reasons.[6] Definitive diagnosis of recurrence requires histological confirmation of the native kidney disease. The latter is often omitted in patients presenting with renal dysfunction and atrophic kidneys, and many patients are classified clinically as "chronic glomerulonephritis" or "hypertensive nephrosclerosis." Allograft biopsies are generally only performed when allograft function deteriorates or if proteinuria develops. Thus, asymptomatic histological recurrence may be missed in the absence of protocol biopsies. Additionally, many transplant biopsies are not routinely submitted for immunofluorescence and electron microscopy, thus potentially underestimating the true incidence of glomerular pathology.[7]

A variety of pathological processes such as ischemia, nephrotoxicity, hypertension, and acute and chronic rejection can induce morphological changes that mimic primary glomerulopathies. Frequently, more than one pathological process is present in transplant biopsies. For example, in one study of posttransplant nephrotic syndrome, 59% of biopsies with recurrent or de novo glomerulonephritis (GN) had superimposed features of chronic allograft nephropathy.[8] Finally, glomerular lesions can occur de novo in the transplanted kidney, and in the absence of histological confirmation of the patient's original disease, these lesions may be misclassified.

FACTORS THAT INFLUENCE RECURRENCE

Multiple factors are known to influence the likelihood of recurrent kidney disease after transplantation. These include the type and severity of the original disease, the age at onset, the source of the donor kidney, and possibly, the immunosuppressive regimen used to prevent allograft rejection. In general, disease recurrence in an allograft implies persistence of an extrarenal pathogenetic stimulus. In certain diseases, modification of the pathogenetic stimulus can prevent or delay recurrence of the disease in the allograft. For example, in Goodpasture syndrome, the presence of circulating antiglomerular basement membrane (GBM) antibodies in high titer at the time of transplantation increases the risk of recurrence in the allograft.[9] Conversely, clinical recurrence is extremely rare if the antibody is undetectable over a 6 to 12 month period prior to transplantation.[9]

The severity of disease in the native kidney influences the incidence of recurrence of certain diseases. For example, in

TABLE 40-1 Estimated Rates of Recurrence of Primary Glomerulopathies and Consequent Graft Loss

DISEASE	RECURRENCE RATE	GRAFT LOSS IN PATIENTS WITH RECURRENT DISEASE
FSGS	~ 30%	~ 50%
MGN	3%-10%	~ 30%
IgA nephropathy	30%-60%	10%-30%
MPGN I	15%-30%	~ 33%
MPGN II	~ 80%	10%-20%
Anti-GBM disease	~ 10%	< 5%

FSGS, focal segmental glomerulosclerosis; *MGN*, membranous nephropathy; *MPGN*, membranoproliferative glomerulonephritis; see text for further details.

TABLE 40-2 Estimated Rates of Recurrence of Secondary Glomerulopathies and Consequent Graft Loss

DISEASE	RECURRENCE RATE	GRAFT LOSS IN PATIENTS WITH RECURRENT DISEASE
Diabetic nephropathy	80%-100%	< 5%
SLE	2%-9%	< 5%
ANCA-associated vasculitis	20%-25%	< 5%
HSP	~ 50%	~ 10%
HUS	25%-50%	40%-60%
Scleroderma	2%-20 %	Unknown
Amyloidosis	20%-33%	Unknown
LCCD	~ 50%	Unknown
EMC	~ 50%	Unknown
Multiple myeloma	~ 27%	< 5%
Fibrillary GN	~ 50%	~ 50%

ANCA, antineutrophil cytoplasmic antibody; *EMC*, essential mixed cryoglobulinemia; *GN*, glomerulonephritis; *HSP*, Henoch-Schönlein purpura; *HUS*, (nondiarrheal associated) hemolytic uremic syndrome; *LCDD*, light chain deposition disease; *SLE*, systemic lupus erythematosus; see text for further details.

focal and segmental glomerulosclerosis (FSGS), a fulminant presentation with a short interval (< 3 years) between diagnosis and development of end-stage renal disease (ESRD) increases the risk of disease recurrence in the allograft.[10,11] With regard to age of onset, recurrence of FSGS is more frequent in younger patients whose primary disease presents before the age of 16 years.[12] Conversely, in Henoch-Schönlein purpura (HSP) recurrence is more frequent in patients who develop their disease after the age of 14 years.[13]

With respect to the source of the kidney, some studies have demonstrated higher rates of recurrent GN in recipients of living as compared to deceased donor allografts.[2] It was therefore postulated that phenotypic characteristics shared by related donor-recipient pairs may render the kidney more susceptible to humoral factors. It should be emphasized, however, that many studies fail to demonstrate an increased tendency to disease recurrence in recipients of living related grafts.[14]

It was anticipated that the introduction of cyclosporin A (CsA) and other calcineurin inhibitors (CI) might reduce the incidence of recurrent disease, given the efficacy of these drugs in the treatment of various forms of GN.[15] However, studies involving large numbers of transplant patients have failed to confirm this prediction.[16] CsA has been reported to modify the course of recurrent GN and slow the rate of graft loss in some patients.[16] The incidence of recurrent GN was not found to be increased by a rapid steroid withdrawal protocol, lending further support to the view that the incidence of recurrence is generally not influenced by the immunosuppressive protocol.[17]

The most comprehensive data on graft loss as a result of recurrent GN derives from an Australian study involving 1505 patients with biopsy-proven GN as a primary cause of ESRD.[5] The incidence of graft loss from recurrent GN was 8% over a follow-up period of 10 years. The diseases with the highest rates of graft loss were FSGS (31%) and type 1 membranoproliferative glomerulonephritis (MPGN) (17%). Both male gender and high pretransplantation panel-reactive antibodies levels were noted to be independent risk factors for graft loss from recurrent disease. Recurrent GN was the third most common cause of graft loss at 10 years posttransplantation, and as previously reported, the relative importance of recurrence as a cause of graft loss increases with time posttransplant.[5]

PRIMARY GLOMERULOPATHIES

Focal Segmental Glomerulosclerosis

Recurrent Disease

Primary or idiopathic FSGS accounts for approximately 10% and 20% of cases of idiopathic nephrotic syndrome in children and adults respectively, and the lesion progresses to ESRD in about 60% of patients.[15] Most authors report a recurrence rate of approximately 30% for first allografts[2,9,14,18–20] and a higher incidence in children.[18,21] The rate of recurrence may be as high as 80% in patients who have previously lost a graft to recurrent FSGS.[11,22] In recent years, a number of genetic mutations in genes encoding for components of the slit diaphragm including *podocin* (*NPHS2*), *a-actinin 4*, and *CD2AP* have been identified in familial FSGS. Patients with familial or sporadic FSGS who have homozygous or compound heterozygous mutations in *NPHS2* are at low risk of recurrence (~8%) whereas the risk may be enhanced in patients with heterozygous mutations for reasons that are not clear.[23] A recent report described recurrence of FSGS associated with *WT1* mutation in a patient with Frasier syndrome.[24]

FSGS has been subclassified into five histological subtypes, and in general it has been noted that the subtype occurring in the renal transplant is similar to the disease type present in the native kidney, lending support to the notion that the subtypes represent distinct clinicopathologic entities.[25] In a study of 21 cases of recurrent FSGS in 19 patients, 15 cases recurred in the same histological pattern as in the native kidney, while 3 variants demonstrated plasticity from native to allograft kidneys in the pattern of recurrence.[25] Collapsing glomerulopathy, an aggressive subtype of FSGS, can recur and occur de novo following transplantation with rapid loss of graft function.[26,27] A recent

comparative study of collapsing FSGS and noncollapsing FSGS in kidney transplants confirmed that the collapsing form is a more aggressive disease, with higher levels of proteinuria, more severe histological manifestations, and a higher rate of graft loss.[28]

Recurrent FSGS presents clinically with heavy proteinuria, often with full-blown nephrotic syndrome and its attendant risk of thromboembolic complications.[19] Recurrence may be evident within days of transplantation, particularly in children.[21,29] Graft failure occurs in as many as 50% of adult patients and is more likely in the presence of nephrotic syndrome.[1,10,22,30,31] Graft loss may be even higher in children, as exemplified in a series by Muller and colleagues in which 5 of 6 grafts with recurrent FSGS were lost.[18] A history of accelerated primary graft loss from recurrence significantly increases the risk of loss of subsequent grafts.[14] Conversely, patients who have had prolonged function of their primary graft, despite recurrent FSGS, may expect a similar, more slowly progressive course in subsequent grafts.[32]

A number of risk factors for recurrence of FSGS have been identified: diffuse mesangial proliferation in the native kidney,[10–12,14] rapid deterioration of renal function in the native kidney (i.e., renal failure < 3 years after diagnosis),[9,10,12,22] and younger age at diagnosis.[9,10,12,20,22] Other less well-established predictors of recurrence are delayed graft function and ethnicity. Some studies have described a lower incidence of recurrence in blacks than in Caucasians.[22,31,32] The routine use of CsA has not reduced the incidence of recurrent FSGS,[14,16,22,32] although some authorities claim that high doses ameliorate the clinical course.[22,33] While some studies have found an increased incidence of graft loss due to recurrence in recipients of living related kidneys, there was no such statistically significant difference found in the large series by Briganti and associates.[5]

Although poorly defined, it is known that a circulating permeability factor(s), possibly of T lymphocyte origin is responsible for the induction of glomerular damage in FSGS.[34] Probably the best evidence that supports the permeability factor hypothesis is the development of proteinuria in anephric kidney allograft recipients within hours of living donor transplant surgery.[35–38] A putative permeability factor of molecular weight between 30 and 50 Kda has been isolated from sera of patients with FSGS that increases glomerular permeability to albumin in vitro.[35–38] Dantal and colleagues showed that immunoadsorption of sera from patients with recurrent FSGS on a protein A column transiently reduced proteinuria by an average of 82%.[36] Furthermore, elute from the protein A column enhanced urinary albumin excretion when injected into rats. A recent report by Savin and associates demonstrated that the permeability factor binds to and is inactivated by galactose in testing in vitro.[39] Administration of galactose both intravenously and orally to a patient with recurrent FSGS significantly reduced the level of permeability factor.[39] Further studies are needed to confirm a benefit of galactose therapy early in the course of recurrent FSGS or indeed as prophylactic treatment in patients at high risk.

Current treatment strategies for recurrent FSGS are designed to inhibit secretion of the putative lymphocyte-derived "factor" (CsA or tacrolimus) and enhance removal by plasmapheresis. As noted earlier, CsA has been reported to reduce proteinuria by some but not all investigators.[22,33] About 50% of patients with recurrent FSGS respond to therapeutic plasmapheresis.[10,11,14,22,35,38,40,41] The latter appears most useful if instituted early in the course of disease before glomerulosclerosis has become established.[35,40] In one study, the use of prophylactic plasma exchange in the week prior to transplantation led to a significant reduction in the rate of recurrence from 66% to 37%.[42] Dall'Amico and colleagues reported a benefit of plasmapheresis combined with cyclophosphamide in a study of 15 patients with recurrence in 18 grafts.[41] Reversal of proteinuria occurred in 9 of 11 treated patients, and a persistent remission was obtained in 7 patients.[41] Encouraging data on the use of preemptive plasmapheresis derives from a study of 10 patients who underwent plasmapheresis in the perioperative period.[43] Seven patients, including three who had lost a prior graft to early recurrence, had no recurrence. Plasma permeability factor activity was not fully predictive of recurrence, suggesting that other pathogenetic mechanisms must also play a role.[43]

Recent reports have described successful treatment of recurrent FSGS with the anti-CD20 monoclonal antibody, rituximab, in conjunction with plasmapheresis.[20,44,45] Others have reported no benefit from this regimen.[46] Canaud recently reported on treatment of 10 cases of recurrent FSGS with an intensive regimen consisting of high dose oral steroids, intravenous cyclosporine, and prolonged plasmapheresis for up to 9 months.[47] Sustained remission was obtained in nine patients and partial remission in the remaining patient. This compared to a 27% induction of remission in a group of 19 historical controls.[47] Further evaluation of this regimen in a larger study population is warranted.

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce proteinuria in patients with recurrent FSGS. In a representative study, administration of ACE inhibitors to nine patients with recurrent disease reduced average proteinuria from 11.1 to 4.22 g/24 hours.[22] It is not established as yet whether they prolong allograft survival. Of note however, Opelz and associates failed to demonstrate any benefit of ACE inhibitors in either patient or graft survival in analysis of 17,209 kidney transplant recipients.[48]

De Novo Disease

Whereas de novo FSGS may be a direct consequence of immune injury, emerging evidence suggests that the disease is, at least in part, triggered by hemodynamic stress in remnant nephrons following injury to the kidney by rejection, ischemia, or CI.[49] In some instances de novo FSGS may be a manifestation of chronic allograft nephropathy.[19] Histologically this lesion is characterized by occlusive vascular changes that primarily involve the glomeruli in the outer cortical region. This observation contrasts with recurrent FSGS where the mild obliterative arteriopathy preferentially involves the juxtamedullary glomeruli. Clinically, de novo FSGS presents with proteinuria and a less aggressive course than recurrent FSGS, but it is nonetheless a negative independent predictor of graft survival.[50] Collapsing GN, the most aggressive subtype of FSGS, has also been described as a de novo lesion in the renal allograft.[27,28]

Membranous Nephropathy

Recurrent Disease

Membranous nephropathy is the most common cause of idiopathic nephrotic syndrome in adults and progresses to ESRD in 20% of cases.[15] Membranous nephropathy may recur in allografts or, more commonly, develop as a de novo lesion.[9] Most studies quote a recurrence rate of 3% to 10%,[51,52] though figures as high as 25% to 57% have been reported.[9,11,53]

Recurrent membranous nephropathy occurs earlier posttransplantation than de novo disease and often runs a more aggressive course. The average time from transplantation to recurrence is 10 months, though appearance as early as one week and as late as 7 years posttransplantation has been reported.[11,51,53] A recent study of 23 patients with membranous nephropathy documented a recurrence rate of 42% on surveillance biopsies. The early histological changes were subtle and the clinical manifestations mild with no proteinuria in three of eight cases and low-grade proteinuria in the remainder.[53] Proteinuria did increase with time, however, and histological progression was noted in two of three patients who underwent repeat biopsies. The typical clinical presentation of recurrent membranous nephropathy is nephrotic-range proteinuria and graft loss is in the order of 30%.[9,51,52] However, many grafts lost to recurrent membranous nephropathy have displayed evidence of other pathological processes such as rejection, and the relative contribution of each process to graft failure is often unclear.[52]

Some studies suggest that a high degree of human leukocyte antigens (HLA) matching between donor-recipient pairs and the use of living related kidneys also increases the risk of recurrence.[51] Furthermore, recurrent disease may manifest earlier (in the first 3 months posttransplantation) in living-related than in cadaveric grafts.[51] The routine use of CsA has not reduced the rate of recurrence,[16] nor have high dose steroids been successful in reducing proteinuria.[51,54] A number of case reports have described successful treatment of nephrotic syndrome secondary to recurrent membranous nephropathy with rituximab.[55,56] Retransplantation may be considered in patients who lose their initial graft, although consecutive recurrent membranous GN has been described.[52]

De Novo Disease

De novo membranous nephropathy is the most frequent cause of posttransplant nephrotic syndrome after chronic allograft nephropathy (see later).[51,54] The reported incidence varies from 0.3% to 6.7%[54] with a higher frequency reported in centers with a policy of routine renal biopsy for assessment of non–nephrotic-range proteinuria. In one study, de novo membranous nephropathy developed in four of seven patients with a second transplant.[57] The incidence of de novo membranous nephropathy increases with time, and as overall graft survival rates improve, it is increasingly recognized as a late complication.[54] De novo disease typically presents later than recurrent disease and manifests with progressive proteinuria. Graft loss may occur in as many as 50% of patients with persistent nephrotic-range proteinuria.[58] However, in many cases, graft loss has been attributed to chronic rejection rather than to membranous nephropathy.[54]

De novo membranous nephropathy is often associated with some degree of vascular rejection and calcineurin inhibitor-induced vasculopathy.[54] An association with chronic viral infection, most commonly hepatitis C, has been demonstrated in up to a third of patients with de novo membranous nephropathy, suggesting a potential viral trigger for immune complex formation.[54,58,59] CsA is not effective in preventing development of the lesion.[16] Similarly, pulse steroid therapy was not effective in reducing proteinuria in larger series, although occasional successes have been claimed.[60]

Immunoglobulin A Nephropathy

Immunoglobulin A (IgA) nephropathy is the most common primary glomerular disease worldwide. Histological evidence of recurrence is reported in 30% to 60% of allografts.[5,9,61–63] IgA deposition alone is not clinically significant unless accompanied by the development of mesangioproliferative changes. A retrospective study of 106 patients with biopsy proven IgA nephropathy demonstrated similar 10-year graft survival compared to 212 patients without IgA nephropathy who were transplanted during the same period.[63] Less commonly, recurrent IgA nephropathy presents as aggressive crescentic disease.[64–66] Tang and associates described 10 cases of crescentic IgA nephropathy in transplant recipients in whom the disease presented with RPGN and progressive loss of renal function with 9 of 10 patients reaching ESRD.[67] Recurrent IgA nephropathy has generally been considered a benign condition that causes graft loss in less than 10% of cases.[11,63] However, recent data suggest that recurrent IgA nephropathy may carry a more adverse prognosis and become an increasingly important cause of graft loss as overall allograft survival improves.[61,63]

The introduction of mycophenolate has not altered the rate of recurrence of IgA nephropathy or attenuated its adverse impact on graft outcome.[68] In contrast, a recent report suggested a significant benefit of induction therapy with antithymocyte globulin (ATG) in reducing the incidence of recurrence.[69] In this retrospective study of 116 patients with IgA nephropathy, the recurrence rate was 41% in the group who received no induction therapy compared to 9% with ATG induction.[69]

Some studies suggest that recurrent IgA nephropathy is more frequent in living compared to deceased donor grafts,[70,71] though this is not a universal finding.[5,61,63] A retrospective study from the ANZDATA Registry found that living related transplants with zero HLA mismatches had a higher incidence of recurrence but similar rates of graft survival compared to living donor transplants with one or more HLA mismatches.[72] This contrasted with the survival advantage seen in recipients of zero mismatched living donor transplants in other causes of GN. It has been suggested that HLA-DR4 positive donors and recipients experience an increased risk of recurrence after living donor transplantation,[73] though analysis of the ANZDATA registry data failed to confirm this.[72] Subclinical IgA nephropathy in the donor may be responsible for IgA deposits in the allograft,[71] and such deposits have been documented to disappear with time.[74]

Other risk factors predictive of recurrence are younger age with patients younger than 30 years having a relative risk of 2.6[63] and the presence of crescentic GN in the native kidney.[70] Conversely, serological abnormalities of IgA, such as aberrantly glycosylated IgA1, were not significantly associated with early recurrence in a study of 30 patients with recurrent IgA nephropathy, but polymorphisms of tumor necrosis factor α (TNF-α) and interleukin-10 (IL-10) were associated with a reduced risk.[75] These findings need validation in prospective studies.

Several therapeutic strategies have been proposed for recurrent IgA nephropathy including combinations of steroids, cyclophosphamide, azathioprine, CsA, or plasma exchange, but without compelling evidence to support their use. A case report documented a benefit of fish oil in significantly reducing proteinuria and preserving renal function in a patient with recurrence of IgA nephropathy in a second kidney transplant.[76] Consistent with the known renoprotective effects of ACE inhibitors in native kidney disease, these agents have recently been reported to have a beneficial effect in reducing proteinuria in patients with recurrent IgA nephropathy.[77,78] A recent retrospective study showed a trend to increased 5 and 10 year graft survival in long-term follow-up of patients with IgA nephropathy treated with ACE inhibitors.[79] It should be noted that data on a much larger population of transplant patients reported by Opelz and associates failed to demonstrate this beneficial effect of ACE inhibitor therapy.[48]

Membranoproliferative Glomerulonephritis Type I

Recurrent Disease

MPGN type I is an immune-complex-mediated GN that frequently follows an indolent clinical course and progresses to ESRD in about 20% of patients.[15] It recurs in 15% to 30% of renal allografts and causes graft loss in one third of these patients.[5,11,80–82] The prevalence of cryoglobulins, hypocomplementemia, and rheumatoid factor positivity is seen less frequently in MPGN after transplantation, perhaps due to concomitant pharmacological immunosuppression.[83,84] Recurrent renal disease presents clinically with heavy proteinuria and microscopic hematuria and may be evident within three weeks of transplantation.[83] Crescentic disease with a rapidly progressive course in the native kidneys, the use of living related kidneys, and loss of a previous graft to recurrent disease have been associated with an increased risk of recurrence.[80–82] Hypocomplementemia persisting after renal transplantation does not appear to be associated with higher recurrence rates.[80]

There are isolated reports in the literature of successful treatment of recurrent disease with increased immunosuppression. One group used long-term plasmapheresis over a 16-month period to maintain renal function along with the administration of monthly-pulsed intravenous cyclophosphamide.[85] Cahen and colleagues successfully induced remission of recurrent disease with a combination of prednisolone, cyclophosphamide, and dipyridamole.[83] Aspirin and dipyridamole may also stabilize kidney function.[80] Rituximab was recently reported to be efficacious in a patient with recurrent MPGN.[86]

De Novo Disease

MPGN accounts for about 33% of cases of de novo GN in renal allografts.[16,84,87,88] The most important etiological factor appears to be chronic hepatitis C infection, which is present in up to 30% of patients with ESRD.[88] Hepatitis C virus (HCV) infection is associated with development of a variety of glomerular lesions in native kidneys including MPGN. HCV positive transplant recipients have an increased incidence of both de novo GN and transplant glomerulopathy compared to HCV negative patients.[89] In a study of 94 HCV positive transplant recipients, de novo MPGN was demonstrated in six of nine patients undergoing renal biopsy for investigation of proteinuria of greater than 1.5 g/day.[87] In another study, de novo MPGN was demonstrated in five of eight HCV positive patients who underwent biopsy for the investigation of proteinuria of greater than 1g/day.[84] Interestingly, cryoglobulinemia was not a prerequisite for the development of MPGN as has also been noted with primary GN in the native kidney. In a report by Ozdemir and associates, 15 of 44 (34%) HCV positive patients developed de novo GN, most frequently MPGN, compared to 6.6% of 121 HCV negative recipients.[89] Short-term graft survival was reduced in patients with de novo GN. Similar results were reported by Cruzado and associates who noted that HCV positivity was an independent predictor of graft loss in patients with de novo GN.[59]

Of interest, Gallay and colleagues described two hepatitis C positive transplant recipients who developed a hybrid lesion with ultrastructural features of both MPGN and chronic allograft nephropathy.[88] This may simply reflect the coexistence of HCV induced GN and allograft rejection, or alternatively it may reflect modification of the morphology of HCV associated GN by immunosuppressive therapy.

The role of interferon α in the treatment of HCV associated MPGN in kidney transplant recipients is controversial because of the risk of precipitating acute rejection.[90] Whereas successful treatment of viral infection and stabilization of kidney function has been reported in occasional patients,[88] interferon α has been shown to trigger acute rejection when used as prophylaxis for cytomegalovirus (CMV)[91] and as treatment for hepatitis C associated liver disease.[92,93] A recent report described successful treatment of three patients with de novo cryoglobulinemia and MPGN with rituximab, though severe infectious complications developed in two patients.[86]

Membranoproliferative Glomerulonephritis Type II

Recurrent Disease

MPGN type II (or dense deposit disease) is characterized pathologically by accumulation of electron dense deposits within the glomerular basement membrane. This disease carries a worse prognosis than type I disease and is much more likely to recur following transplantation.[15] Recurrence has been documented in up to 80% of allografts.[9,11,40] In a study of 75 pediatric recipients from the North American Pediatric Renal Transplant Cooperative Study database, the overall 5 year survival of patients with type II MPGN was

significantly lower than the overall rate in the database as a whole.[94] The rate of graft loss due to recurrent disease at 5 years was 15%. There was no excess graft loss in living donor recipients.[94] In one study, the observed increased frequency of recurrence of Type II MPGN was accounted for by virtue of more severe disease with more mesangial proliferation and a greater number of crescents on the original biopsy in these patients. This led the authors to conclude that it is disease severity and not the subtype of MPGN that dictates the risk of recurrence.[82] The rate of graft loss from recurrence is in the order of 10% to 20%,[9] although a 50% graft failure rate was reported in one series of 10 transplant recipients with recurrent disease.[40] Recurrence of disease in a second graft after loss of the first allograft to recurrence has also been described.[11]

Recurrence usually presents within the first year posttransplantation. Despite the high rate of histological recurrence, clinical manifestations are absent in 40% of patients. The remainder present with proteinuria and slowly progressive allograft dysfunction. It appears that graft loss is more likely in male patients who present with nephrotic-range proteinuria and rapidly progressive GN.[40] Unlike patients with native disease, most patients with recurrence do not have circulating C3 nephritic factor, probably a reflection of immunotherapy. The use of CsA has generally not been found to influence the rate of recurrent MPGN, apart from one study, which suggested a reduced incidence.[95] Treatment of recurrent dense deposit disease has generally been ineffective, as in native disease. One isolated report described clinical and pathological improvement with the use of plasma exchange.[96]

Antiglomerular Basement Membrane Disease

Anti-GBM nephritis accounts for less than 2% of GN causing ESRD.[15] Recurrence, as defined by the reappearance of linear immunoglobulin G (IgG) deposition along the glomerular capillary walls, has been reported to occur in up to 55% of patients. However, only 25% of these patients have clinical manifestations of recurrent disease, and graft loss is rare.[11] Given the compelling evidence that anti-GBM antibodies are pathogenic in this disease, it is standard practice to delay transplantation for a 6 to 12 month period after this serum marker is undetectable.[97] A recent report described a patient with recurrent anti-GBM disease in whom intensive immunosuppressive therapy including plasmapheresis and rituximab failed to salvage the graft.[98] Of note, this patient was transplanted after 3 years on hemodialysis (HD) but continued to have low levels of anti-GBM antibody at the time of transplant.

De Novo Crescentic Glomerulonephritis

De novo crescentic GN is rare in renal allografts, the most common setting being anti-GBM nephritis developing in allografts of patients with Alport syndrome. The autoantigen in anti-GBM nephritis is a 28 kd component of the α3 chain of type IV collagen.[99] In X-linked Alport syndrome, a mutation in the gene encoding the α5 chain of type IV collagen is associated with abnormal assembly of the α3 chain of type IV collagen.[100] Anti-GBM antibodies may develop when the immune system of Alport patients encounters the Goodpasture antigen in the allograft for the first time. Whereas asymptomatic linear deposition of anti-GBM antibody is most the most common finding, full-blown rapidly progressive GN and graft loss can rarely occur.[101,102]

In a review of 30 patients with Alport syndrome who were transplanted, patient and graft survival rates were similar to those of an age-matched control group.[103] Five of 15 grafts examined histologically were positive for linear IgG deposition; however, crescentic nephritis was not seen. Two patients underwent repeat biopsies. Linear IgG deposition had disappeared in one after 12 months, but persisted in the second patient 5 years later.[103] The survival of the IgG positive and negative grafts was similar, as was the level of renal function. A single case of recurrent crescentic GN in a second allograft in an Alport patient who had already lost the first graft to anti-GBM disease has been described.[102] In this patient, renal function stabilized following plasmapheresis and an increase in the dose of CsA.

Development of de novo crescentic GN is very rare in patients with ESRD due to diseases other than Alport syndrome.[104] In one report, de novo crescentic GN developed early in association with glomerular basement membrane deposition of IgG.[104] The author proposed that exposure of the allograft to a circulating antibody, perhaps contained in antilymphocyte globulin, may have contributed to the development of this lesion. Treatment of de novo crescentic GN is similar to that for disease in the native kidney. Success has been claimed with early use of cyclophosphamide, plasmapheresis, steroids, and dipyridamole;[102,104] however, others dispute the long-term effectiveness of treatment.[105]

SECONDARY GLOMERULOPATHIES

Diabetes Mellitus

Diabetic nephropathy (DN) is the leading cause of ESRD and accounts for about 20% of renal transplants performed annually in North America. Diabetic kidney disease in a transplant may be recurrent or, less commonly, de novo disease. As with native diabetic kidney disease, DN presents with proteinuria and a slow deterioration of renal function over 15 to 20 years. However, it is an uncommon cause of graft failure mainly because of patient death with a functioning graft or failure of the graft from other causes.[106–108]

Renal biopsy may reveal glomerular basement membrane deposition of IgG as the sole abnormality in the early posttransplant period. However, the classical histological changes of diabetic nephropathy, such as glomerular basement membrane thickening, mesangial expansion, and arteriolar hyaline deposition, may been seen within 2 to 4 years of transplantation.[109,110] In a retrospective series of 58 patients, Bhalla and associates found that 40% of patients had histological evidence of diabetic nephropathy of which 69.6% were recurrent and 30.4% were de novo DN.[111]

As with native diabetic kidney disease, glycemic control is a critical determinant of the rate of progression of recurrent DN. In a prospective randomized study of 48 type I diabetes mellitus (DM) renal transplant recipients, Barbosa and colleagues showed that tight glycemic control was associated with fewer histological changes of diabetic nephropathy.[112] The same effect is seen in patients receiving simultaneous

pancreas-kidney transplantation where achievement of euglycemia cures diabetes and prevents the development of DN in the transplanted kidney.[113,114] Control of blood pressure and proteinuria are also vital to preserving renal function, but while there is compelling evidence to support the use of ACE inhibitors in native kidney disease, a metaanalysis by Opelz and associates failed to demonstrate improved graft and patient survival in transplant recipients on ACE inhibitors.[48,115,116] However, this metaanalysis did not examine the effect of these agents in proteinuric diabetic kidney disease.[48]

Systemic Lupus Erythematosus

Despite advances in the therapeutic options for systemic lupus erythematosus (SLE), lupus nephritis still accounts for 1% of cases of ESRD. Following kidney transplantation there appears to be a reduction in lupus activity.[117,118] It is not clear whether this represents the natural history of SLE or the impact of continuous immunosuppression. The rate of recurrence of lupus nephritis postrenal transplantation varies from 2% to 9%.[3,119,120] In the landmark study of recurrent GN by Briganti and coworkers, 81 of 1505 transplant recipients had a primary diagnosis of lupus nephritis, but no instance of graft loss from recurrence of lupus nephritis was seen.[5] Similarly, of the nine cases (8.4%) of biopsy proven disease recurrence described by Stone and colleagues, only four (3.8%) proceeded to graft loss.[119] When disease does produces significant renal dysfunction it usually responds to increased immunosuppression.[121]

Overall, patient and graft survival rates following kidney transplantation for lupus nephritis compares favorably with transplantation for other causes of ESRD.[5,117,119,120,122] Lochhead and associates documented significantly improved graft and patient survival in recipients of living donor grafts suggesting that the latter may be preferable in this population.[123] However, it is of paramount importance to screen prospective living donors for hematuria and proteinuria prior to transplantation, because there is a 1.5% rate of occurrence of lupus in first degree relatives.[124] A small increased risk of recurrent lupus nephritis in recipients of living related kidneys was suggested by the review of Mojcik and associates but was not confirmed in other reports.[117,119] Bunnapradist and associates identified a lower risk of graft failure in deceased-donor transplant recipients who received mycophenolate mofetil (MMF) but no differences in outcome with calcineurin inhibitors or induction therapy.[122]

Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Antineutrophil cytoplasmic antibody (ANCA)-associated renal diseases comprise of Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and renal-limited crescentic GN.[125] All may be associated with a relapsing and remitting course, and ESRD occurs in up to 20% of patients.[125,126] Many patients with ANCA-associated vasculitis undergo kidney transplantation and experience graft and patient survival rates comparable to those observed in patients with ESRD from other diseases. Both renal and extrarenal manifestations can recur several years following transplantation.[5,127,128] Patients with renal recurrence of ANCA vasculitis typically present with hematuria, an active urine sediment, and deteriorating graft function. Most of the data on disease recurrence derives from case reports and small case series with reported recurrence rates of up to 20%; however, recurrence is a rare cause of graft failure.[127,128] Gera and colleagues reported on 20 patients with microscopic polyangiitis and 15 patients with Wegener granulomatosis who underwent renal transplantation and were treated with antibody induction, corticosteroids, MMF, and tacrolimus.[129] While three patients developed extra renal relapse, there was no reported recurrence of renal vasculitis during a 5 year follow-up period.

In a study by Nachman and coworkers, the relapse rates of microscopic polyangiitis or renal limited crescentic GN were similar to Wegener granulomatosis and there was no difference in recurrence between patients with proteinase-3-specific ANCA and myeloperoxidase-specific ANCA.[127] Renal transplantation should be delayed until disease is inactive as patients with active disease at the time of transplant appear to have a higher rate of relapse.[130] Persistence of isolated ANCA positivity is not a contraindication to renal transplantation as a preoperative ANCA titer does not appear to correlate with the risk of recurrence.[127,129] Of the reported 35 patients reported by Gera and associates, 15 had positive ANCA titers at the time of transplantation and none developed disease recurrence. Similarly, the reappearance of ANCA or a rising ANCA titer following transplantation does not accurately predict disease recurrence.[131]

The optimal immunosuppressive regimen posttransplantation in patients with ANCA-associated renal diseases has not been determined. It is likely that immunosuppression administered to prevent graft rejection helps prevent disease relapse. Indeed, the data by Gera and associates would suggest that modern immunosuppression may be more protective against relapse.[129] Recurrent disease usually remits following treatment with pulsed intravenous methylprednisolone and cyclophosphamide,[127,131] and a recent case report demonstrated remission with rituximab.[132]

Henoch-Schönlein Purpura

HSP is an immune-complex disorder characterized by skin, joint, abdominal, and renal involvement. The pathological hallmark of the disease is deposition of IgA in the glomerular mesangium and blood vessels of the dermis and intestine. The incidence of histological recurrence following renal transplantation is approximately 50%.[1,13,133] This incidence is similar to IgA nephropathy, a disease that may be a renal-limited form of HSP.[133]

Recurrent HSP is usually benign and may be subclinical with the diagnosis established by the finding of mesangial hypercellularity and IgA deposition on renal biopsy. Active proliferative nephritis with or without extrarenal manifestations has been reported in up to 20% of cases.[13,134] In a retrospective study, Moroni and colleagues reviewed 17 adult patients with ESRD secondary to HSP who received 19 renal transplants and were followed for a mean of 9 years post transplantation.[134] Eight grafts demonstrated histological evidence of HSP recurrence, and the median time to recurrence was shorter in HSP compared to IgA

nephropathy (30 months vs. 52 months).[134] Patients with crescentic GN on their native kidney biopsy and a rapid progression to renal failure had a significantly higher rate of recurrent disease and graft failure.[134] Similarly, case reports and small case series have shown that patients with active extra renal involvement can develop disease recurrence resulting in graft failure.[13,135] For these reasons, a waiting period of 6 to 12 months after resolution of purpura is generally advised before proceeding with transplantation.[4,11] However, even with these precautions, recurrence may be observed as illustrated in a series by Meulders and associates, where two patients with recurrence had been on dialysis for 22 and 37 months prior to transplantation.[13]

Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

Hemolytic uremic syndrome-thrombotic thrombocytopenic purpura (HUS-TTP) is a spectrum of disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, intravascular coagulation, and kidney failure with thrombotic microangiopathy seen on biopsy. Besbas and associates recently classified HUS-TTP into two groups: HUS-TTP where there is a specific known cause and a second group where the cause is unknown.[136] The first group includes infection-induced disease, disorders of complement regulation and disorders of von Willebrand proteinase (ADAMTS13) deficiency while the second group includes idiopathic disease and HUS-TTP associated with CI therapy.[136] HUS-TTP is commonest cause of acute renal failure in young children but is a rare cause of ESRD in adults. HUS-TTP can recur after kidney transplantation or occur as de novo disease.

Recurrent Disease

The reported recurrence rate of HUS after renal transplantation varies widely from as low as 9% to as high as 73%.[137–139] Recurrence is less likely in diarrhea-associated HUS than in non-diarrhea-associated HUS, which might explain the lower incidence of recurrence in children where the disorder is more frequently associated with Shiga toxin.[138,140] In a review of 36 renal grafts in 27 patients with HUS-TTP and complement factor H mutations, 73.7% of patients had disease recurrence with greater than 80% progressing to graft loss within 22 months.[141] Of note, the specific type of mutation was not predictive of recurrence of HUS or graft loss.[141] Similarly poor graft outcomes were identified in a metaanalysis of 10 studies comprising 159 grafts in 127 patients with recurrence of HUS-TTP.[142]

Artz and colleagues identified a higher incidence of acute rejections in those with HUS recurrence.[138] There are conflicting reports as to whether CI increase the risk of recurrence.[16,137,138,141] Small case series have suggested that other immunosuppressive agents may predispose to recurrence, including antilymphocyte globulin (ALG)[139] and OKT3.[143] In a metaanalysis by Ducloux and associates, older age at onset of HUS, short duration between disease onset and ESRD or transplantation, and use of living related donors were identified as additional risk factors for recurrence.[142] In one report using pooled data from several series, a much lower rate of recurrence was found in patients who had undergone pretransplant bilateral nephrectomies than in those whose native kidneys were in situ.[144]

Typically recurrent HUS-TTP presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Management of recurrent HUS is essentially the same as for primary disease, involving plasma exchange or intravenous immunoglobulin, or both.[145,146] There is some anecdotal evidence regarding the use of rituximab in patients who fail to respond to plasma exchange.[147] In patients on CI, the dose should be either reduced or preferably withdrawn at the first sign of recurrence.[137]

De Novo Disease

De novo HUS-TTP developing postrenal transplant is much rarer and has a more variable clinical presentation than seen with recurrent disease. The most important risk factors are the use of CI (cyclosporine and tacrolimus) or mTOR inhibitors (sirolimus), or both.[1,142,148] Schwimmer and coworkers reported on 21 renal transplant recipients with histological evidence of de novo HUS-TTP and noted that the majority of cases were associated with CI use.[148] Patients with systemic disease were more frequently treated with plasma exchange and dialysis and had a higher rate of graft loss.[148]

De novo HUS-TTP typically occurs in the early posttransplant period. It is proposed that CI may induce endothelial cell injury through a number of prothrombotic mechanisms resulting in thrombotic microangiopathy.[149] It has also been hypothesized that ischemia-reperfusion injury, acute vascular rejection, and viral infection may trigger de novo HUS.[1,150] Other risk factors identified for de novo HUS not included younger recipient age, older donor age, female gender, and previously unidentified complement deficiencies.[151,152]

De novo HUS is associated with reduced graft survival. Management involves reduction or withdrawal of causative agent where appropriate.[153] Treatment of de novo HUS is based on regimens for disease in native kidneys.

Systemic Sclerosis

Renal involvement scleroderma presents either as rapidly progressive renal failure with malignant hypertension and oliguria (scleroderma renal crisis) or as a slowly progressive chronic kidney disease characterized by proteinuria and hypertension. Overall scleroderma is a rare cause of ESRD, and consequently the literature on kidney transplantation in this condition is limited.

Transplantation in scleroderma is associated with poorer graft and patient outcome than in other causes of ESRD.[154,155] A case series of 115 patients reported lower patient and graft survival rates when compared to the general transplant population. However, the survival of patients with scleroderma and ESRD was superior after transplantation when compared to dialysis.[154] Older reports indicate that the rate of recurrence after transplantation was as high as 30%, although more recent reports suggest lower rates.[4,154,156] The strongest predictor of recurrent scleroderma appears to be aggressive primary disease with a time interval from onset of systemic sclerosis to ESRD of less than one year.[154,156]

There are no clear guidelines on optimal immunosuppression in scleroderma posttransplant. A small case series

suggested a potential association between high dose glucocorticoids and CI and an increased risk of recurrence; thus alternative regimens using low dose steroids, MMF, and sirolimus may be used.[157] Graft survival can be maximized by ensuring that the patient is free of active disease at the time of transplantation and by aggressive control of hypertension posttransplantation. Early reports suggested that bilateral nephrectomy at the time of transplantation improves outcome. However such recommendations are rarely necessary given improvements in antihypertensive therapy.[4]

GLOMERULAR DEPOSITION DISEASES

Amyloidosis

Light chain (AL) and secondary (AA) amyloidosis are systemic disorders that frequently involve the kidney, leading to ESRD. Very few of these patients progress to renal transplantation because of the mortality associated with amyloidosis, especially in those with AL type amyloidosis, particularly with cardiac involvement.[158] The majority of patients with amyloidosis who undergo renal transplantation have AA amyloidosis.[158] Amyloid deposits recur in 8% to 26% of grafts in patients who survive for longer than 12 months.[4,11,159]

Graft loss due to recurrence is uncommon. In a recent retrospective study of 13 patients with 16 renal grafts, graft survival at 1 and 5 years was 56% and 56%; however, the major cause of graft loss was death with a functioning graft.[160] These findings of reduced patient survival have been shown in several series and reflect ongoing systemic disease, especially cardiac disease.[158]

No specific therapeutic strategies have been identified for recurrent disease. In a retrospective study of 21 patients with familial Mediterranean fever (FMF) and ESRD secondary to amyloidosis, colchicine was found to be of benefit in preventing or delaying development of recurrent amyloidosis post renal transplant.[161]

A novel approach to the management of ESRD as a consequence of AL amyloidosis was described by Leung and associates, who performed living donor kidney transplantation to restore renal function, followed by an autologous stem cell transplant in five patients.[162] At a mean follow-up of 18 plus or minus 9 months, none of the five patients showed clinical or laboratory evidence of recurrent AL disease, and all had stable renal function. This experimental therapy is a promising development for the future. Despite the risk of recurrence and the relatively high mortality rate, patients with amyloidosis should nonetheless be considered for transplantation, because survival appears superior with renal transplantation compared to maintenance dialysis.

Monoclonal Gammopathies

Lymphoplasmacytic disorders may cause renal insufficiency through a variety of pathological mechanisms. Chief among these are AL amyloidosis (see earlier), light chain deposition disease (LCDD), myeloma cast nephropathy, and fibrillary-immunotactoid GN (see later).[159,163,164] Rarer manifestations include Fanconi syndrome and heavy chain deposition disease. It is difficult to make strong inferences about the outcome of transplantation in these disorders, because the information available is limited to case reports.

LCDD recurs in at least 50% of allografts and is associated with severe renal impairment and loss of graft function.[165,166] The majority of cases have kappa chain deposition, although a single case of lambda light chain deposition recurrence has been reported.[167] De novo LCDD without evidence of malignancy has been reported in a renal allograft 16 years after successful renal transplantation.[168] Rituximab has been shown in a single case study to delay disease recurrence.[169]

Myeloma is generally deemed to be a contraindication to transplantation because of the high risk of exacerbating disease with immunotherapy. Nevertheless, case reports have shown a low rate of recurrence of cast nephropathy that appeared to have little adverse affect on graft function.[170,171] However, a number of patients died from recurrent extra renal disease or sepsis, illustrating the poor prognosis in this disease. De novo multiple myeloma in renal allograft recipients has been reported.[172,173] In one of these patients, the myeloma was associated with LCDD in the allograft.[173]

Fibrillary-Immunotactoid Glomerulopathy

Fibrillary-immunotactoid glomerulopathy is a rare disorder that is characterized by extracellular deposition of Congo-red negative, nonbranching microfibrils or microtubules within the glomerular mesangium and capillary walls in the absence of light chains or cryoglobulins.[174] Clinically, fibrillary GN presents with proteinuria, hematuria, and hypertension with progression to ESRD occurring within the course of months to a few years (50% after 5 years). Experience with transplantation in these patients is limited. From the small number of cases reported, it appears that fibril deposition recurs in at least 50% of patients; however, the decline in renal function in allografts is usually slower than in native kidneys, and many patients maintain satisfactory function over years.[164,174] In small case series by Pronovost and associates, and Samaniego and associates, disease recurrence did not lead to early graft loss.[164,175]

In a recent study of 12 patients with a diagnosis of ESRD secondary to fibrillary GN, investigators determined that seven patients had evidence of a coexisting monoclonal gammopathy.[176] Interestingly, all of the five cases of recurrence were detected in patients with coexisting monoclonal gammopathy with none identified in fibrillary GN alone.[176]

NONGLOMERULAR DISEASES

Oxalosis

Oxalosis or primary hyperoxaluria type 1 is an autosomal recessive disease, which results from deficiency of hepatic peroxisomal alanine glyoxylate aminotransferase. Absence of this enzyme causes oxalate overproduction and recurrent calcium oxalate nephrolithiasis and nephrocalcinosis.

Because the metabolic defect is confined to the liver, combined liver and kidney transplantation can restore normal oxalate levels and is considered the treatment of choice for children with oxalosis complicated by progressive renal

disease and evidence of marked tissue oxalate deposition. Since 1984 more than 100 such combined procedures have been performed with a 5 year actuarial survival of 80% for patients and 71% for liver grafts with stable renal function.[177]

Following kidney transplantation alone, oxalate levels remain high and disease recurrence commonly results in graft loss.[18] In five patients with ESRD secondary to oxalosis, Muller and coworkers reported recurrence in four patients, all of whom progressed to graft failure.[18] In a larger case series, Broyer and associates reported on 98 kidney transplant recipients, 31% of whom developed recurrent renal oxalosis that resulted in graft failure.[178] Several measures have been recommended to maximize successful engraftment: First, renal replacement therapy should be instituted early (once the GFR approaches 20 ml/min) to limit tissue oxalate deposition, which will be released into the circulation and deposited in the allograft posttransplant.[179,180] Aggressive preoperative dialysis is recommended to deplete the extrarenal tissue oxalate pool.[181] It is beneficial to establish a brisk postoperative diuresis, because deposition of oxalate in the allograft seems to be accelerated during periods of delayed graft function.[181] The use of a living donor allograft and avoidance of the immediate use of CI may also be helpful. Administration of pyridoxine, a coenzyme that functions in the conversion of glyoxylate to glycine and thereby decreases the glyoxylate pool, has also been recommended to maintain graft function.[182]

Cystinosis

Cystinosis is an autosomal recessive disorder that results from defective transport of cystine from lysosome to cytosol. Lysosomal accumulation of cystine in the renal interstitium ultimately causes interstitial fibrosis, glomerular sclerosis, and renal failure. Renal transplantation is very successful and is the preferred mode of treatment for children with this condition.[4,183,184] Cystinosis and cystine-induced tubular cell dysfunction per se does not recur.[4,183,184] However, cystine-laden cells, probably host macrophages, can be found in the transplanted kidney.[4,183,184] Despite successful renal transplantation, the systemic effects of pretransplantation cystine accumulation in other organs persists and accounts for ongoing morbidity.

Fabry Disease

Fabry disease is a rare X-linked lysosomal storage disorder. It is due to deficiency of the lysosomal enzyme alpha-galactosidase that leads to the accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb3), in lysosomes of most cells and tissues of the body. Life expectancy is markedly reduced in males with Fabry disease, and death from cardiac or renal disease typically occurs in the fourth and fifth decade of life.

Early reports of kidney transplantation in this population indicated very poor outcomes; however, more recent evidence indicates better results: Shah and colleagues identified 81% and 74% 5-year patient and graft survival rate at 5 and 10 years posttransplant in 197 kidney transplant recipients, while Inderbitzin and associates reported graft survival rates of 90% and 66% respectively in 10 patients.[185,186] Despite excellent graft survival, Fabry patients have a higher risk of death that likely relates to the increased cardiovascular risk associated with this disease.[185]

It was initially thought that renal transplantation would cure renal disease in Fabry disease as the donor kidney would produce normal amounts of alpha-galactosidase. However, biopsy studies have demonstrated recurrence of Fabry disease manifested by Fabry inclusions in the vascular endothelium and deposition of glycolipid in tubular epithelial and endothelial cells as early as six months posttransplantation.[187] Typically disease recurrence does not lead to graft failure but, as for diabetes mellitus, this may be because the graft fails from other causes or patients die from cardiac complications before the disease reaches ESRD.[185]

The Fabry Outcome Survey examined the use of enzyme replacement therapy (ERT) post kidney transplantation in 20 out of 35 Fabry patients.[188] Patients receiving ERT had higher glomerular filtration rates and lower proteinuria, although the significance of this finding is unclear, because there was no difference in graft outcomes.[188]

Sickle Cell Disease

Approximately 4% of patients with sickle cell disease progress to ESRD.[189] Experience with transplantation is limited but recurrent disease appears to be relatively common, although graft loss is rare.[190,191] Graft loss may result from an acute vasoocclusive crisis or from the more indolent effect of recurrent sickling episodes. Secondary focal sclerosis has been described in transplanted kidneys, presumably a consequence of nephron loss due to intrarenal sickling.[191] An increased incidence of sickling crises has been described following renal transplantation, possibly due to the increased hematocrit and blood viscosity that follow successful engraftment. Crises appear to be more common following transplantation in homozygotes than in heterozygotes.[190] There is a suspicion that OKT3 induces sickling crises in some patients and this agent should be used with caution in this setting.

CHRONIC ALLOGRAFT NEPHROPATHY

Chronic allograft nephropathy (CAN) is a term used to describe a gradual decline in renal function with histological evidence of interstitial fibrosis and tubular atrophy occurring at least three months posttransplant and where no specific cause can be identified. It is the most common cause of graft loss after the first year posttransplantation and is evident by histology in 60% of patients 2 years posttransplant.[192,193] Clinically, CAN may be asymptomatic; it more usually presents with proteinuria and progressive impairment of renal function. In a study of 74 renal transplant recipients with nephrotic syndrome, 42% had CAN on renal biopsy.[8]

Nankivell and colleagues identified two phases of renal parenchymal damage in serial biopsies of 120 patients with ESRD from diabetes mellitus following combined kidney and pancreas (n = 119) or kidney transplant alone (n = 1).[114] An initial phase of tubulointerstitial damage

arose from ischemic injury, prior severe rejection and subclinical rejection, while later changes were characterized by microvascular and glomerular injury. CI were associated with increasing glomerulosclerosis and further tubulointerstitial damage. Severe chronic allograft glomerulopathy was present in 58% of patients at 10 years.[114]

Immunosuppression regimens appear to be of central importance in management. Several studies have shown that a decrease or withdrawal of CI can stabilize or improve renal function.[194–197] Ciancio and associates found that a tacrolimus and MMF regimen was associated with a trend toward better graft function and fewer episodes of acute rejection in 150 first renal transplant recipients.[198] In the Creeping Creatinine study, the addition of MMF and withdrawal of CsA resulted in a significant improvement in graft function with no increased risk of acute rejection.[196] The role of ACE inhibitors and ARBs in CAN remains unclear. A retrospective study of 63 patients with biopsy proven CAN demonstrated improved renal function with ACE inhibitors and ARBs.[199] However, these findings were not supported by Opelz and colleagues.[48]

A full list of references are available at www.expertconsult.com.

Chapter 41

PEDIATRIC RENAL TRANSPLANTATION

William E. Harmon, M.D.

ROLE OF TRANSPLANTATION

Chronic dialysis and renal transplantation are both effective treatments for end-stage renal disease (ESRD). The majority of adults with ESRD are receiving dialysis rather than undergoing renal transplantation, although the number seeking renal transplantation continues to rise.[1] There is a survival advantage of transplantation for virtually all candidates. Unfortunately, the lack of suitable donors has limited the number of people who can receive transplants. Renal transplantation was recognized as the better form of treatment for children with ESRD 2 decades ago,[2] and it is known to provide a survival benefit for this population.[3] Both peritoneal dialysis and hemodialysis lead to growth deceleration. Data from the dialysis component of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry[4] show that the overall height deficit of −1.8 standard deviation (S.D.) became more negative, reaching a value of −2.16 S.D. after 2 years of dialysis. Additionally children do not tolerate being dependent on any modality, and maintenance dialysis induces loss of self-esteem and emotional maladjustment.[5] Also, cognitive achievement testing may deteriorate with prolonged time on dialysis.[6] In contrast, the mobility and freedom from dietary restrictions afforded by a functioning renal transplant enable children to live nearly normal lives. Although renal transplantation has not lived up to the promise of normal growth for all children, dramatic short-term improvements in height can be seen in many, and final adult height is improving after transplantation.[7–10] Most importantly, successful transplantation permits the child to attend school and to develop normally. School function testing improves dramatically following transplantation.[11,12] Importantly, young children now have the best long-term outcomes of all ages of transplant recipients, verifying the utility of transplantation in this age group.[13] For all of these reasons, successful renal transplantation remains the primary goal of programs that care for children with ESRD. Pediatric recipients of kidney transplants have the highest percentages of living donors (LDs), and they receive substantial preference on the deceased donor (DD) transplant waiting list,[14] leading to very short waiting times. Thus pediatric patients with ESRD should not have substantial delays in undergoing renal transplantation after developing ESRD.

Incidence and Frequency of Pediatric Renal Transplantation

In 2008, about 16,500 kidney transplants were performed in the United States, and about 800 of these were in children younger than 18 years, suggesting that pediatric patients comprise about 5% of all transplant recipients. Although the number of pediatric transplants performed each year has generally varied by no more than 10%, the donor origin has undergone substantial changes. The Scientific Registry of Transplant Recipients (SRTR) data show that living kidney donation has expanded substantially and the number of LDs exceeded the number of DDs for the first time in 2001.[15] However, the number of LD rose slightly until 2004 and has fallen since that time, while the number of DD has continued to increase. Living donation now accounts for 36% of all kidney transplants in the United States.

A change in DD allocation has greatly reduced the waiting time for children and led to a surge in DD transplants (Figure 41-1). Although has this change has undoubtedly led to more rapid transplantation for these children, there may be a decrease in mean graft survival rates related to this shift.[16] Parents comprise the majority of LDs. Mothers comprise the majority of parent donors; fathers account for 46%. Since there are more boys than girls who receive kidney transplants, it should not be surprising that fathers donate to sons 64% of the time and mothers to sons 60%. There is no outcome advantage to either parent, with the possible exception that infants younger than 1 year of age seem to have fewer rejections if the mother is the donor.[17,18]

Because children most often have siblings who are too young to donate (less than 18 years), the NAPRTCS registry has recorded only 305 transplants between siblings. Of these, 150 grafts were from donors younger than 21 years of age. A review of the NAPRTCS registry identified only 12 LDs younger than 18 years of age, of which 11 were transplants between siblings and one was from parent to an infant. It is quite clear that most programs are very reluctant to use minor donors.[19,20] However, a review of United Network for Organ Sharing (UNOS) data revealed that from approximately 40,000 LDs in the United States between 1987 and 2000, 60 were from donors younger than 18 years of age.[21] Twenty-four of the recipients were children and 36 were adults; only 7 of the transplants were between identical twins.

In recent years there has been a substantial interest in living-unrelated donation in adult transplant literature, because the outcome of the grafts has been shown to be better than that of DD kidneys.[22] NAPRTCS identified 123 instances of living-unrelated donation between 1987 and 2001. In a preliminary analysis of the first 38 living-unrelated recipients, 23 (61%) were male, 30 (79%) were Caucasian, 8 were younger than 6 years old, and 20 were older than 12 years.[23] This was the primary transplant for 29 of the 38 recipients. Of the 38 donors, 22 were non-biological parents, and a family friend was the donor in 10 of the cases. In 2008, UNOS documented 293 pediatric

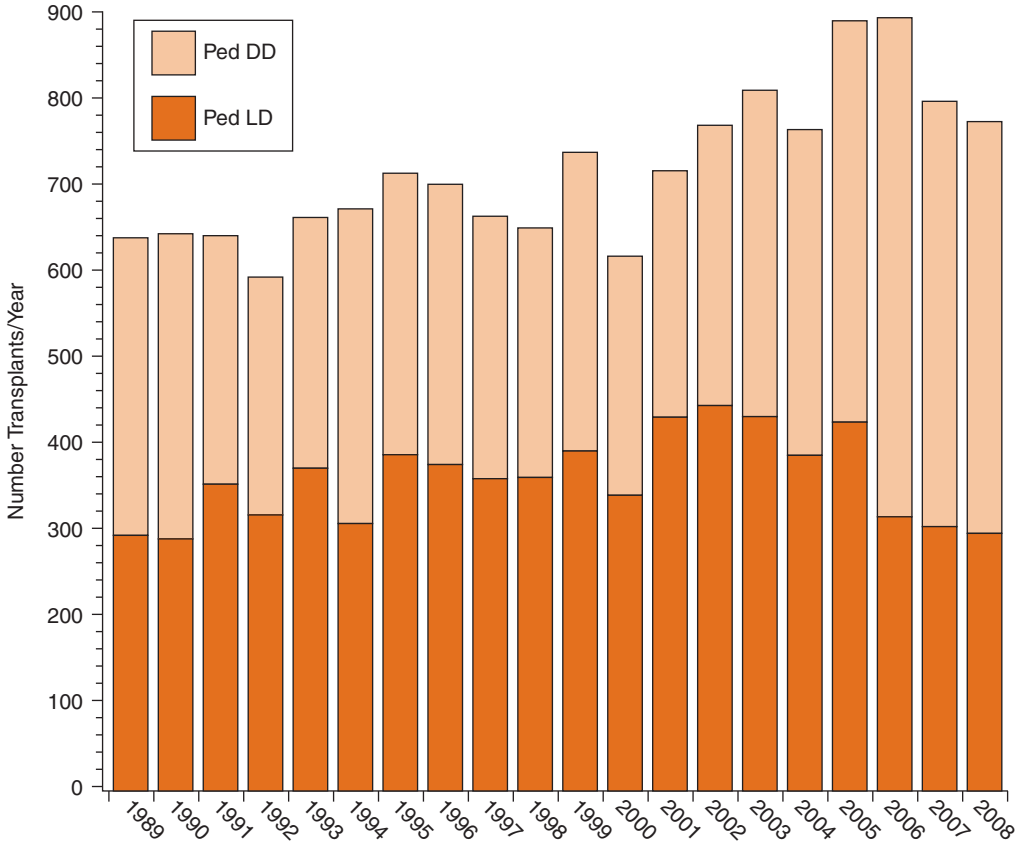


FIGURE 41-1 Number of living donor (LD) and deceased donor (DD) kidney transplants in children younger than 18 years of age by year from 1989 to 2008. (Adapted from United Network for Organ Sharing [UNOS] data. Available at: www.unos.org.)

LD kidney transplants: 189 (68%) were from parents, 24 from siblings, and 30 from other biologically related donors. Thus 83% of LD kidney transplants in children came from biologically related donors. Thirty-five LD came from other unrelated, nine from paired exchanges, and six from anonymous donors.

The majority of DD kidneys for children are recovered from adult donors. In the 1980s there was a tendency to preferentially place kidneys recovered from infants into infant recipients, with disastrous consequences for patient and graft survival.[24] As a result of widespread dissemination of these data,[25,26] there has been a marked change in the practice. From 1987 through 1990, the percentage of DDs older than 10 years ranged from 59% to 68%. From 1991 through 1994, these percentages ranged from 78% to 88% and have continued to rise to greater than 90%. Prior to 1991, children younger than 2 years of age comprised 3.2% of DDs. In 1991, no pediatric recipient received a kidney from a DD younger than 2 years of age; and in 1995 and 1996, there were no such kidneys used in children.[27] Between 1991 and 2007, less than 1% (28/3,385) of DD for children were younger than 2 years of age.[28] This change in allocation of kidneys from young donors led to improvement in graft survival.[24] Some specialized pediatric programs have reported good results with young donors,[29] but many programs reserve grafts from very young donors for en bloc transplantation into older recipients.[30]

Etiology of End-Stage Renal Disease in Children

ESRD in children is generally due to congenital or inherited diseases. In reviewing 7651 transplants in the NAPRTCS database, the most common congenital diagnoses found are aplastic/hypoplastic/dysplastic kidneys, and obstructive uropathy, with each representing about 16% of the patients (Table 41-1).[31] Among glomerular disorders, focal segmental

TABLE 41-1 Pediatric Kidney Transplant Gender and Race

		DISTRIBUTION BY PRIMARY DIAGNOSIS				
DIAGNOSIS	TOTAL	N 9854	% 100	% MALE 60	% WHITE 64	% BIOPSIED 56
Aplasic/hypoplastic/dysplastic kidney		1564	16	62	67	30
Obstructive uropathy		1538	16	85	68	30
Focal segmental glomerulosclerosis		1154	12	58	48	94
Reflux nephropathy		515	5.2	43	79	35
Chronic glomerulonephritis		328	3.3	43	50	75
Polycystic disease		287	2.9	52	77	52
Medullary cystic disease		271	2.8	50	88	66
Hemolytic uremic syndrome		260	2.6	56	81	52
Prune belly		254	2.6	98	63	38
Congenital nephrotic syndrome		254	2.6	53	70	87
Familial nephritis		225	2.3	80	62	72
Cystinosis		201	2	54	90	45
Pyelo/interstitial nephritis		173	1.8	48	78	76
Membranoproliferative glomerulonephritis—type I		171	1.7	44	60	97
Idiopathic crescentic glomerulonephritis		171	1.7	34	57	95
Systemic lupus erythematosus nephritis		150	1.5	17	27	95
Renal infarct		136	1.4	48	81	37
Berger (IgA) nephritis		127	1.3	54	71	94
Henoch-Schönlein nephritis		110	1.1	41	75	85
Membranoproliferative glomerulonephritis—type II		81	0.8	51	80	96
Wegener granulomatosis		55	0.6	46	78	93
Wilms tumor		52	0.5	58	68	92
Drash syndrome		52	0.5	58	79	92
Oxalosis		52	0.5	54	91	75
Membranous nephropathy		44	0.4	61	54	93
Other systemic immunological disease		32	0.3	13	62	93
Sickle cell nephropathy		16	0.2	56	0	75
Diabetic glomerulonephritis		11	0.1	36	36	64
Other		962	9.8	52	64	64
Unknown		608	6.2	53	33	34

(Adapted from J.M. Smith, D.M. Stablein, R. Munoz, et al., Contributions of the transplant registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], Pediatr. Transplant. 11 [4] [2007] 366-373.)
CNI, calceneurin inhibitor.

glomerulosclerosis (FSGS) is the most common; 1154 children received a renal transplant for FSGS between 1987 and 2007. The primary diagnosis also varies with the race of the recipient. Caucasian children account for 64% of all recipients; however, Caucasian children account for less than 50% of the children transplanted for FSGS. The data regarding the role of FSGS leading to ESRD can be better appreciated by observations from the dialysis section of the registry, in which the two most common diagnoses are FSGS and aplastic/dysplastic kidneys at 14% each. Of 733 children with FSGS on dialysis, Caucasian children account for only 34%, with African American and Hispanic children accounting for 62% of the patients. Twenty-four percent of African American children on dialysis, and 30% of those older than 12 years of age have FSGS. Table 41-1 shows the primary diagnoses by gender and race of 9854 children who received a transplant as recorded by NAPRTCS since 1987 and the percentage of biopsy proven diagnoses. It is important to observe that the biopsy confirmation of the primary diagnosis was made in 94% of FSGS, in 87% of systemic immunological diseases, and in 90% of congenital nephrotic syndrome patients. The information regarding primary diagnosis is critical in predicting graft survival and recurrence of the original disease, as discussed later.

Indications for Renal Transplantation in Children

There has been a substantial change in long-term renal allograft outcome for children during the past decade.[32–34] Previously young children were thought to have poor short- and long-term graft survival related to several factors, most prominently a proposed heightened immune response, especially in infants.[35,36] The most recent comprehensive registry reviews have clearly demonstrated a dramatic reversal in outcomes with marked improvements in patient and kidney graft survival for infants and young children.[32,33,37] Indeed, several analyses have identified these very young recipients as now having the best long-term survivals of all age groups (Figure 41-2).[17,32,38,39] Thus, children of all ages are excellent transplant candidates. Therefore, by the time that the child has reached chronic kidney disease (CKD) stage 4 to 5, planning for kidney transplantation and pretransplant preparation should have begun. There are very few contraindications to kidney transplantation in children. Perhaps the only two are presence of another otherwise-fatal condition with a short projected survival, such as metastatic Wilms tumor and severe neurological compromise. About 75% of children are treated with a course of chronic dialysis prior to renal transplantation, but unless there is a need for specific pretransplant preparation, there is no advantage to pretransplant dialysis. As in adults, preemptive renal transplantation has indeed been associated with a survival advantage.[40]

PRETRANSPLANT PREPARATION

Recipient Age at Transplantation

Kidney transplantation prior to 6 months of age or in a recipient who weighs less than 6 kg is exceptional. Since 1987, NAPRTCS has recorded 94 transplants performed in children younger than 12 months.[31] Of these, seven transplants were performed in children between 3 and 5 months of age, 22 were performed in children between 6 and 8 months, and 63 were performed in children between 9 and 11 months. Only 17 infants have been transplanted since 2000. Since infants and adolescents have different risk factors for both patient and graft survival, children frequently have been grouped into five age categories: 0 to 1 year, 2 to 5 years, 6 to 12 years, 13 to 17 years, and 18 to 21 years of age. In 1987 25% of all pediatric transplants were performed in children 0 to 5 years of age,[35] whereas in 1995 the same age group accounted for 15%.[27] Whether the decreased number of transplants in this group is due to a perception of their vulnerability or to the development better dialysis has not been established. It is important to note that excellent results have been obtained in very young patients in some individual centers.[38,41] The concept of a heightened immune response in young recipients is controversial.[42–44] Thus the unique problems associated with transplantation

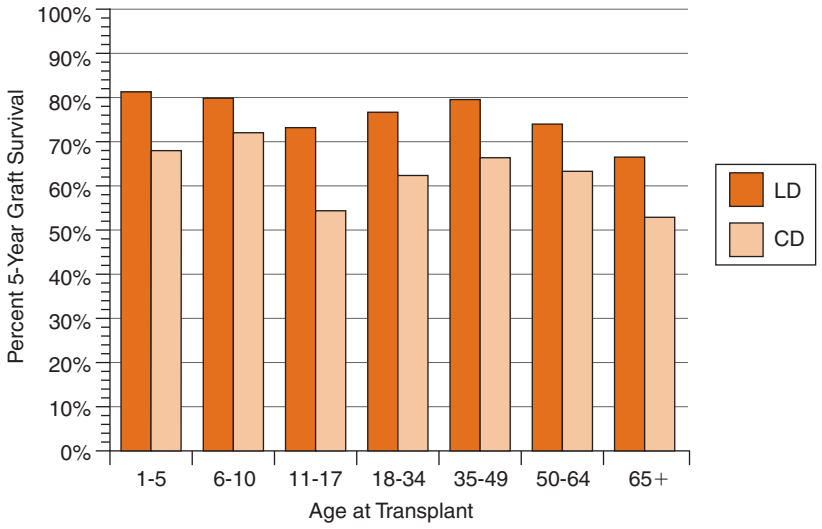


FIGURE 41-2 Five-year actuarial graft survival following LD and DD renal transplantation in children and adults by recipient age. Young children currently have the best long-term outcomes of all age groups. (Adapted with permission from P.M. Colombani, S.P. Dunn, W.E. Harmon, et al., Pediatric Transplantation, Am. J. Transplant. 3 [Suppl. 4] [2003] 53-63.)

in young recipients may be related to infections, technical issues and differences in pharmacokinetics[17,45–48] rather than their immune response.

There has been a substantial change in long-term renal allograft outcome for children during the past decade.[32–34] Previously, young children were thought to have poor short- and long-term graft survival related to several factors, most prominently a proposed heightened immune response, especially in infants.[35,36] Conversely, however, adolescents were subsequently noted to have a higher rate of late acute rejections,[17] and infants may have a lower rate of acute rejection than older children.[45] An important analysis of the UNOS data demonstrated that short-term pediatric renal transplant survival rates became comparable to those in adults about 10 years ago.[17] The most recent comprehensive registry reviews have clearly demonstrated a dramatic reversal in outcomes. Improvements in surgical technique,[49–53] donor selection,[54] immunosuppression practices,[55–59] the enhanced experience of specialized pediatric transplant teams,[60] and the development of multicenter research consortia have all led to marked improvements in patient and kidney graft survival for infants and young children.[32,33,37] Indeed, several analyses have identified these very young recipients as now having the best long-term survivals of all age groups.[17,32,38,39] In fact, young recipients of adult-sized kidneys who have immediate graft function have been reported as having the longest projected graft half-lives, exceeding even those of adult recipients of 2-haplotype matched LD transplants.[61]

Currently, pediatric recipients younger than age 11 who receive LD kidney transplants have 3-year graft survival rates that are as good or better than older age groups (93% for those aged 0 to 5 years and 92% for those aged 6 to 10 years).[39] The results of young recipients of DD kidney transplants are similar to those seen in adults, with recipients aged 1 to 5 years and those aged 6 to 10 years having 3-year graft survival rates of 82%.[39] Unfortunately, this excellent outcome is not seen in adolescents whose 3-year graft survivals for both LD (85%) and DD (76%) grafts are worse than all other age groups. As shown in Figure 41-2, 5-year graft survival rates for both LD and DD kidney transplants for children less than 11 years of age are better than all other age groups of children and adults.[39]

Recipient Preparation

Before a child can undergo renal transplantation, the problems caused by CKD must be addressed and optimized if possible. In those cases where ESRD is due to urological abnormalities, corrective reconstructive surgery should be undertaken, especially to the lower urinary tract, prior to transplantation. Two of the major consequences of CKD are anemia and growth retardation, both of which should be addressed prior to transplantation. A recent report of final adult height in pediatric renal transplant recipients suggests that the current improvement in final adult height posttransplantation is more related to improving height deficits prior to transplantation than to any net gains achieved after transplantation.[9,62] Uremia also leads to wasting and malnutrition in the child, and this can compromise the success of the procedure. For example, prophylactic native nephrectomy and reversal of protein wasting and malnutrition improves the outcome of transplantation in children with congenital nephrotic syndrome.[63–65] Careful preparation is particularly important in children undergoing preemptive transplants. Since live-viral vaccines are generally not indicated in chronically immunosuppressed patients, children should receive all appropriate vaccines pretransplantation. While guidelines exist for the evaluation of the adult transplant recipient,[66,67] there are no similar published reports for pediatric patients.

Urological Preparation

Children with the developmental diagnoses described in Table 41-1 require a thorough urological evaluation prior to transplantation, and they frequently require pretransplant reconstructive urological surgery. In a NAPRTCS report, 1878 of 7651 (25%) pediatric transplant recipients were identified as having lower urinary tract abnormalities.[37] For all such patients, a history of voiding pattern prior to development of renal failure is most helpful. Preliminary investigations consist of measurement of urinary flow rate and ultrasound estimation of the postmicturition urine volume. Urinary flow rate should be at least 15 ml per second,[68] and the residual volume should be less than 30 ml. Further investigations would consist of urethrocystoscopy in patients suspected of a urethral stricture, and a voiding cystometrogram is essential for complete assessment of bladder function.[69] This provides information about bladder capacity, pressure rise, and the efficiency of voiding. Still more information can be obtained by combining the urodynamic studies with radioisotope imaging. Routine voiding cystourethrogram is not indicated in older patients with no symptoms related to the urinary tract.[70]

A bladder with a very small capacity may not be adequate for a functioning transplant. Occasionally a small-capacity bladder may be seen in patients with prolonged oligoanuria. However, if the bladder is distensible and the bladder wall compliant, such a bladder may be used safely for kidney transplantation. Other criteria for a useable bladder are an end-filling pressure less than 30 cm of H_2O, and a good flow rate. In patients with a poor flow rate, if urethral and bladder outlet obstruction are ruled out, the problem may be due to detrusor malfunction.[68] When a bladder fails to empty completely, infection and obstruction are potential complications that may shorten graft survival. Intermittent, clean, self-catheterization, which is widely used in urological practice, can be safely used posttransplantation in patients where the primary abnormality is an inefficient and uncoordinated detrusor function.

Most pediatric patients have a urinary bladder that will adapt to the new kidney. Although the bladder may not appear to have the capacity, especially in patients on long-term dialysis prior to transplantation, it will most often distend with usage.[71] However, in patients with a truly low capacity or high pressure bladder augmentation may be necessary prior to transplantation.[72–74] The goal of modern reconstructive pediatric urology is to have a competent low-pressure urinary reservoir that can be emptied by voiding or at least by intermittent catheterization. Augmentation cystoplasty consists of adding bowel or gastric wall to the bladder, whereas substitution cystoplasty is performed when most of the bladder is excised and replaced with bowel. Gastric remnants have been popular for augmentation; however,

they do tend to cause excessive loss of acid in the urine, leading to discomfort and metabolic alkalosis.

Early attempts to reconstruct bladders with bioengineered material are ongoing. There are promising reports of *bioengineered* bladder material, although these have not yet been tried in transplant recipients.[75,76] Urological reconstruction, including augmentation cystoplasty, typically occurs prior to transplantation;[74,77–84] some programs have also reported successful reconstruction after transplantation.[85] In patients in whom augmentation has been performed, long-term antibiotic therapy and intermittent catheterization may have to be carried out to prevent urine stasis and infection. In general, the incidence of urinary tract infection and other complications is higher in these recipients; however, their course is generally no worse than pediatric recipients without urological abnormalities.

If native kidneys in children with ESRD are causing hypertension, chronic infections, or excess losses of protein, urine, or other substances, there should be serious consideration for nephrectomy prior to or at the time of transplantation.[86] About 25% of children have native nephrectomies prior to transplantation.[87]

Donor Preparation

Donor Selection

The selection of the appropriate donor is an integral part of the transplantation procedure and may be a limiting factor in the long-term outcome of kidney transplantation for any individual child. The use of LDs has generally been much more common in pediatric kidney transplantation than in adults.[26,27,31,32,37,39,87] In general, the choice of a LD is a good one because, on average, graft survival can be twice as long when a LD is used compared to a DD.[16,31,32,87] There are limitations to the use of LDs however, such as donor suitability, blood group incompatibility, and age; thus not every child may have a suitable LD. Moreover, there is concern about using LDs when there is a substantial risk of early graft failure or recurrent disease.[88,89] When DDs are used for children, careful attention should be paid to using low-risk donors since the mortality risk for children after kidney transplantation is low and children are expected to require the grafts for long periods of time.[14,54,90–92]

THE TRANSPLANTATION PROCEDURE

Technical Issues in Transplantation

The operative technique differs based on the weight of the child. For small children, less than 15 kg, the transplant is performed through a midline incision, and the large abdominal vessels are used.[71] After reflection of the right colon, the aorta and the inferior vena cava are exposed.[93] The aorta is mobilized from above the inferior mesenteric artery to the external iliac artery on the right side. After ligating and dividing the lumbar branches, the iliac arteries and the inferior mesenteric are encircled. Next the inferior vena cava is mobilized from the left renal vein to the iliac veins. After ligating the lumber veins, the iliac veins are encircled. The donor renal vein is anastomosed to the recipient vena cava in an end-to-side technique.[94] The donor renal artery is then anastomosed to the recipient aorta in an end-to-side fashion. Careful attention needs to be paid to the recipient hemodynamic response upon clamping and unclamping of the major vessels, and it is desirable to maintain a central venous pressure of 15 to 18 cm H_2O prior to unclamping.[71,93] The perfusion of the transplanted kidney may be slow due to the fact that a large adult kidney will take up a significant portion of the normal pediatric blood volume. Hemodynamic studies suggest that the cardiac output of infants must double to perfuse the adult donor kidney adequately.[95] Thus volume replacement is critical (Figure 41-3). The ureteral anastomosis is performed by implanting the donor's ureter into the recipient's bladder using either a Politano-Ledbetter procedure or a modification of it to assure nonrefluxing anastomosis. Many surgeons now prefer a nonrefluxing extravesical rather than transvesical approach for ureteroneocystostomy because it is faster, a separate cystotomy is not required, and less ureteral length is necessary, thus assuring a distal ureteral blood supply.[96–98]

The transplantation technique used in children with a body weight greater than 15 kg is similar to that employed in adults. Unlike the transperitoneal approach necessary in younger children, this transplant is extraperitoneal, with the renal vein anastomosed to the common iliac or the external iliac vein.[93] The arterial anastomosis can be to either the common iliac or internal iliac artery. The ureterovesicular anastomosis is performed using the techniques described earlier.

Evaluation of Graft Dysfunction

At the completion of the vascular anastomosis and release of the vascular clamps, immediate function of the transplanted kidney is demonstrated by the production of urine. Various causes however, may prevent initial function, and evaluation

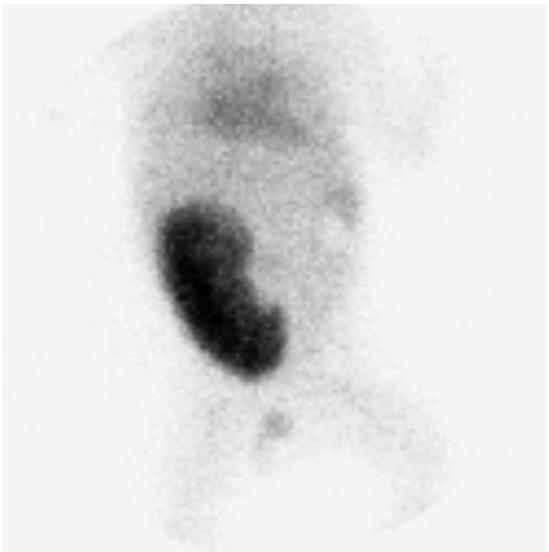


FIGURE 41-3 ^{99M}Tc-MAG3 radionuclide renal scan in a 9-month-old infant who received a LD renal transplant from his father. The graft is intraperitoneal and occupies most of the right side of the peritoneal space. Note the relative sizes of the graft and the heart.

of immediate nonfunction and the differential diagnosis of this condition is a critical component of the transplant physician's role (see Chapter 36).

Delayed Graft Function

A well-functioning kidney graft should lead to normal renal function within 2 to 3 days. The lack of attainment of normal renal function, as demonstrated by a fall of the serum creatinine to normal levels, is termed delayed graft function (DGF). There is no consensus concerning the definition of DGF.[99] In some settings, DGF is used only to distinguish recipients who require dialysis after transplantation, but that is a very stringent definition. Acute tubular necrosis (ATN) represents the most frequent cause of immediate graft nonfunction. Data from the NAPRTCS 1996 Annual Report showed that ATN was observed in 5% of LD and 19% of DD transplants.[27] Since the NAPRTCS definition for ATN is stringent, requiring the use of dialysis in the first posttransplant week, these figures probably underrepresent the actual incidence of ATN. The risk of early ATN is related to factors such as prior transplants, prolonged cold ischemia, absence of prophylactic antibody therapy, and the use of more than five pretransplant blood transfusions. The diagnosis is confirmed in most cases by Doppler sonography or the use of radionuclide scan (Figure 41-4). If recovery of graft function is delayed, however, a transplant biopsy may be necessary, because other diagnostic tests cannot distinguish between ATN and rejection or recurrence of primary disease.[100–102] Importantly early acute rejection can mimic ATN or coexist with it.[103] The presence of ATN does not auger well for the transplant, particularly for recipients of DD grafts since graft failure and death are more common under such circumstances.[104,105]

The NAPRTCS data shows that 71% of DD grafts without ATN were functioning at 4 years compared with only 51% of those with ATN.[106] DGF is an independent risk factor for graft loss and death.[107–109] Importantly, although the incidence of DGF is increased when a donation after cardiac death (DCD) donor is used, the detrimental affect of DGF on long-term outcomes in this setting does not appear to be as severe as when it occurs after living donation or after transplantation from brain-dead DDs.[99]

Graft Thrombosis

Graft thrombosis is an almost unique complication of pediatric transplantation. Although usually a major cause of immediate graft nonfunction, it can be seen later on in the course and has been recorded to occur as late as 15 days posttransplantation following initial engraftment and function. Graft thrombosis has been the third most common cause of graft failure in pediatric renal transplantation[37] and may rise to second as acute rejection rates continue to fall (Table 41-2).[31,110] The critical nature of this complication can be appreciated from the fact that it accounts for 10% of graft failure in index transplantation and 12% in repeat transplants in the NAPRTCS registry. A dreaded event, this condition is irreversible in most cases and necessitates removal of the graft. Graft thrombosis should be suspected in cases where there has been immediate function followed by the development of oligoanuria. The diagnosis is established by sonography or radionuclide scan using diethylenetriamine pentaacetic acid (DTPA) or MAG3,[111] which reveals a photopenic defect with no uptake by the transplant kidney (Figure 41-5).

Since the outcome of graft thrombosis is uniformly dismal, numerous studies have been conducted in an attempt to understand and anticipate this complication. The etiology of graft thrombosis is multifactorial, but it is more commonly seen in young recipients.[92] In a special study of 2060 LD and 2334 DD kidneys,[112] the NAPRTCS has shown that a history of prior transplantation increases the risk, whereas increasing recipient age has a protective effect for LD kidneys. The prophylactic use of antilymphocyte antibody also decreases the risk, and this may be particularly true for the monoclonal interleukin 2 receptor (IL-2r) antibodies.[113] For DD kidneys, a cold ischemia time longer than 24 hours increases the risk of thrombosis. The use of antibody induction therapy, the use of donors older than five years of age, and increasing recipient age were factors that decreased the risk of thrombosis. A heightened thrombotic state has also been implicated.[111,114,115] One study showed that centers that performed fewer infant transplants had higher rates of graft thrombosis[60] and another suggested that pretransplant use of peritoneal dialysis increased the risk of thrombosis.[116,117] Some centers routinely administer anticoagulants to pediatric recipients at high risk of graft thrombosis, but no clinical studies of their effectiveness have been performed and its use is not without complications.[118] This incidence of graft thrombosis had not changed over almost 15 years;[37] however, a preliminary report suggests that a new approach to induction therapy by using IL-2r antagonists may be beneficial.[113]

Obstruction, Urinary Leak, and Urological Complications

An uncommon but correctable cause of immediate graft dysfunction is obstruction of the urinary flow, which presents as decreasing urine output and the development of

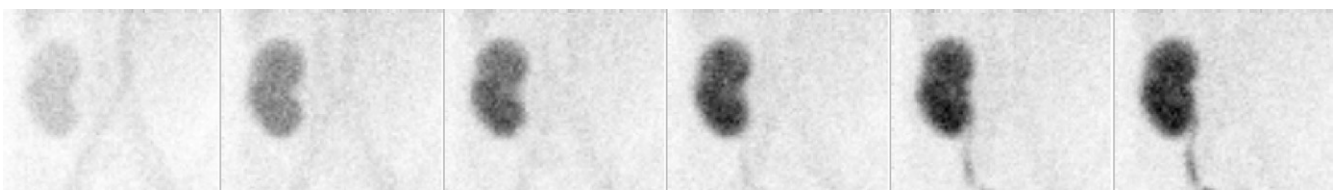


FIGURE 41-4 ^{99M}Tc-MAG3 radionuclide renal scan of a DD renal transplant in a 15-year-old boy performed on the first postoperative day. The cold ischemia time exceeded 24 hours and the recipient experienced oliguric ATN. Note the good perfusion, followed by little excretion and "wash out" of the tracer from the graft.

TABLE 41-2 Cause of Graft Failure

	INDEX GRAFT FAILURES		SUBSEQUENT GRAFT FAILURES		ALL GRAFT FAILURES	
TOTAL	N 2427	% 100	N 320	% 100	N 2747	% 100
Death with functioning graft	226	9.3	23	7.2	249	9.1
Primary nonfunction	60	2.5	2	0.6	62	2.3
Vascular thrombosis	243	10	38	11.9	281	10.2
Other technical	29	1.2	4	1.3	33	1.2
Hyperacute rejection < 24 hours	14	0.6	4	1.3	18	0.7
Accelerated acute rejection	33	1.4	8	2.5	41	1.5
Acute rejection	318	13.1	42	13.1	360	13.1
Chronic rejection	847	34.9	118	36.9	965	35.1
Recurrence of original disease	156	6.4	31	9.7	187	6.8
Renal artery stenosis	15	0.6	0	0	15	0.5
Bacterial/viral infection	45	1.9	5	1.6	50	1.8
CNI toxicity	11	0.5	0	0	11	0.4
De novo disease	8	0.3	2	0.6	10	0.4
Patient discontinued medication	113	4.7	8	2.5	121	4.4
Malignancy	32	1.3	2	0.6	34	1.2
Other/unknown	277	11.4	33	10.3	310	11.3

(Adapted from J.M. Smith, D.M. Stablein, R. Munoz, et al., Contributions of the transplant registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], Pediatr. Transplant. 11 [4] [2007] 366-373.)

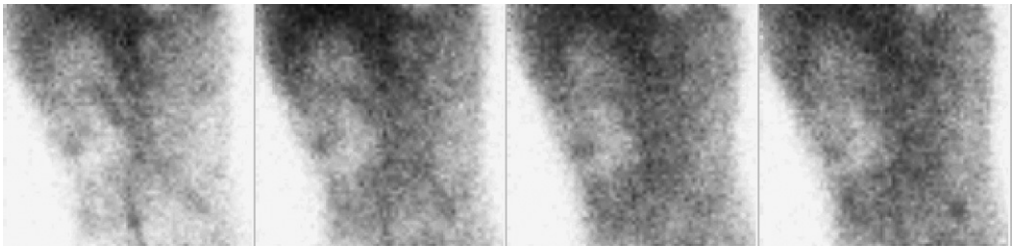


FIGURE 41-5 ^{99M}Tc-MAG3 radionuclide renal scan in a 6-year-old girl with FSGS who received a LD renal transplant, performed 16 hours postoperation. Note the photopenic area in the right abdomen, indicating thrombosis of the graft with no perfusion.

hydronephrosis. An ultrasound or radionuclide scan with a furosemide washout enables the clinician to establish this diagnosis. Obstruction can be due to kinking of the ureter, to edema or blockage of the implantation site of the ureter or to development of a lymphocele. A more ominous cause of immediate nonfunction is the rare case of urinary leak due to disintegration of the distal ureter or rupture of the bladder. This condition is extremely painful due to the extravasation of urine into the pelvis or peritoneal cavity and is established by radionuclide scan (Figure 41-6). The appearance of the tracer in the peritoneal cavity or in the scrotal, vulvar, or inguinal area clinches the diagnosis and immediate surgical correction is necessary.

Immunosuppression Strategies

Two thirds of pediatric kidney transplant recipients receive antibody-based induction therapy following kidney transplantation, with the majority of those receiving IL-2r antagonists.[31] Additionally, most children receive triple maintenance immunosuppression with tacrolimus, mycophenolate mofetil (MMF), and steroids.[31,90] As shown in the NAPRTCS annual report, the "typical" immunosuppression protocols have changed frequently over the past 2 decades (Figure 41-7). However, it also appears as if children who begin treatment under one combination stay on that regimen (Figure 41-8). Several recent multicenter research efforts have been directed toward an attempt to decrease the number of types of chronic immunosuppression, with corticosteroids and calcineurin inhibitors (CNI) being the most common medications targeted for removal.[119] Several single-center[119–122] and multicenter trials[123–125] have reported success in avoiding or withdrawing corticosteroids, although some of these have had substantial adverse effects.[123,126,127] There have also been reports of avoidance of CNI in children, a move designed to prevent nephrotoxicity. At least one of these trials resulted in excellent long-term graft function, but had a high rate of early acute rejections.[128] A subsequent trial with enhanced antibody induction may have better short-term results.[129]

ALLOGRAFT DYSFUNCTION

In the absence of tolerance, the renal allograft is destined for loss by some form of rejection. Rejections are classified as hyperacute (occurring immediately upon grafting), accelerated

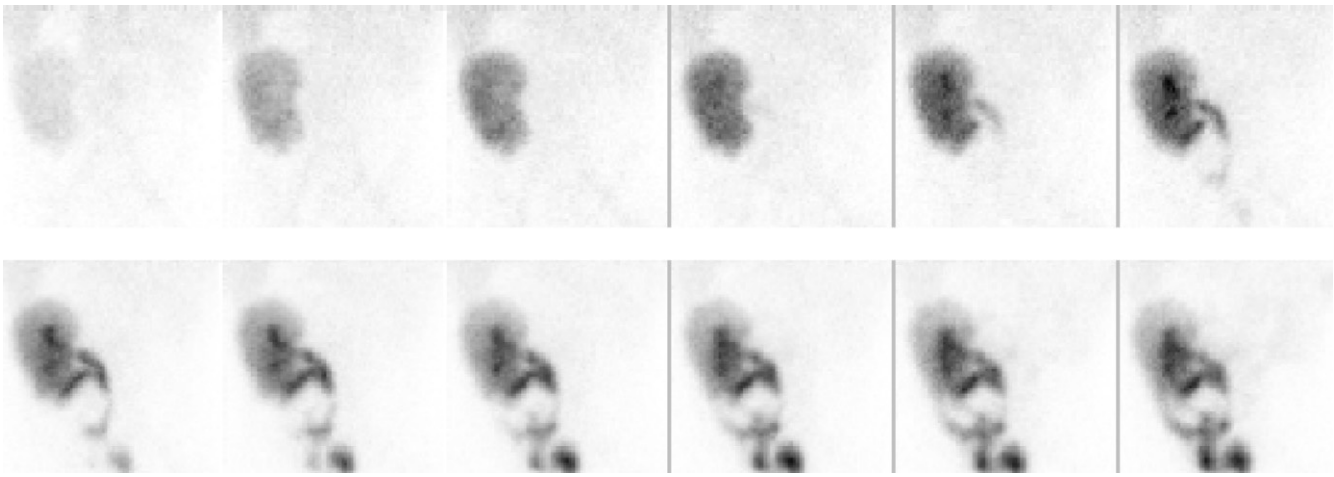


FIGURE 41-6 ^{99M}Tc-MAG3 radionuclide renal scan in an 8-year-old girl who received a DD renal transplant, performed 12 hours postoperation. Note the good perfusion of the graft and the rapid concentration and excretion from the kidney. Tracer, however, rapidly accumulates in the right lower quadrant, outside of the bladder. Investigation demonstrated a traumatic bladder rupture.

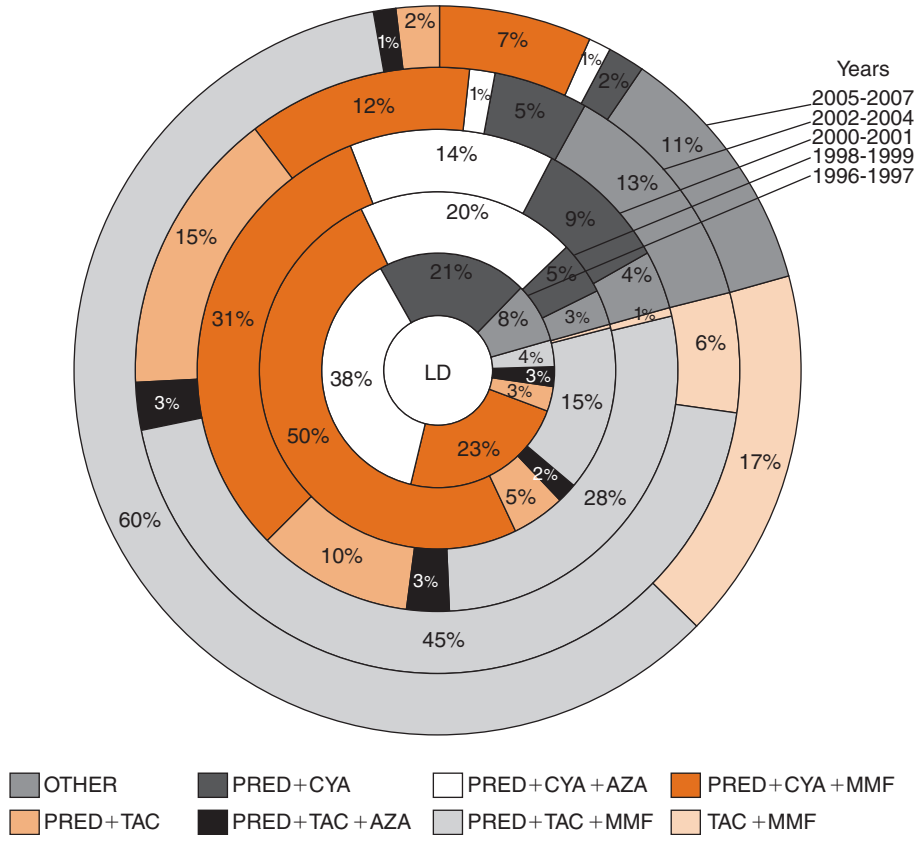


FIGURE 41-7 Maintenance immunosuppression in pediatric LD renal transplant recipients by 2- and 3-year cohorts:1997-2007. (Adapted from North American Pediatric Renal Transplant Cooperative Study NAPRTCS: 2008 Annual Report. Available at www.naprtcs.org.)

acute (occurring within the first week after transplantation), acute (generally occurring within the first year of transplantation), late acute (occurring after the first year), and chronic, for which the time sequence is difficult to establish, because it may occur as early as three months, but generally occurs years later in the course of the transplant. The original disease that caused the native kidneys to fail may also affect the transplanted kidney.

Hyperacute Rejection

Hyperacute rejection is the result of specific recurrent anti-donor antibodies against human leukocyte antigen (HLA), ABO, or other antigens.[130] Irreversible rapid destruction of the graft occurs. Histologically there is glomerular thrombosis, fibrinoid necrosis, and polymorphonuclear leukocyte infiltration. In the early years of transplantation, when the

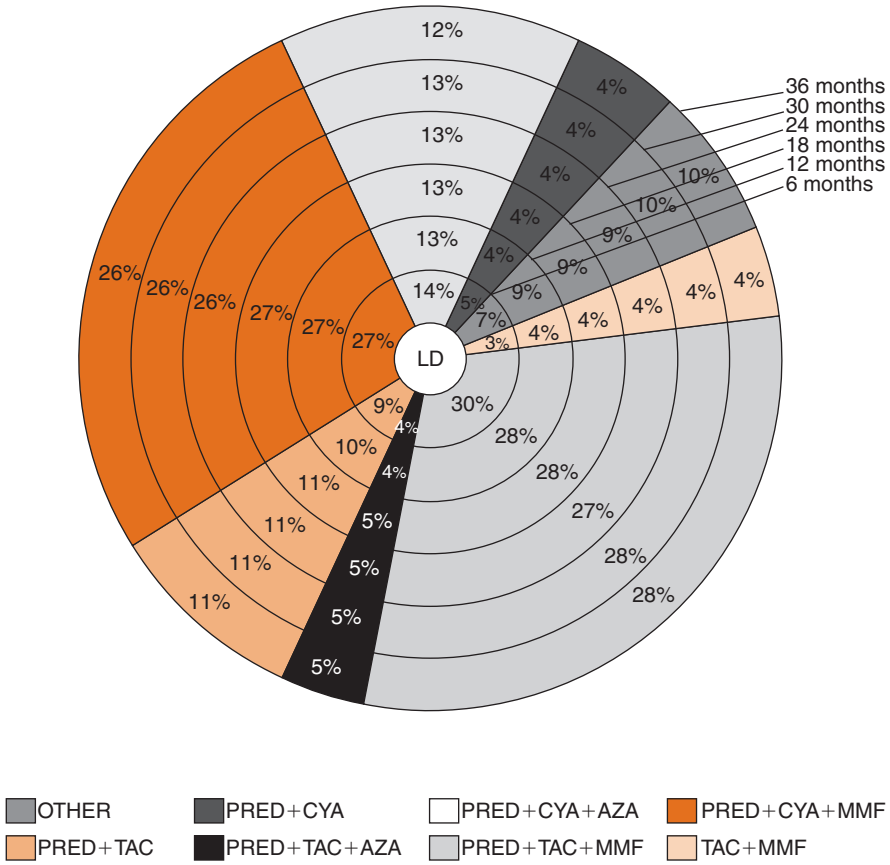


FIGURE 41-8 Maintenance immunosuppression in pediatric LD renal transplants by follow-up time cohorts between 6 and 36 months. (Adapted from North American Pediatric Renal Transplant Cooperative Study: NAPRTCS Annual Report. Available at www.naprtcs.org.)

HLA matching techniques were not well-developed, hyperacute rejection was more common. In most centers, it occurs very rarely. The latest data from the NAPRTCS shows the incidence of hyperacute rejection to be less than 0.25% (17 cases) over the last 15 years. The only treatment is surgical removal of the allograft.

Acute Rejection

Information regarding the incidence and outcome of acute rejection in pediatric renal transplantation is available from the NAPRTCS data. Since NAPRTCS receives data from multiple centers that use different diagnostic and treatment protocols, the definition of a rejection episode is based upon the circumstance of a patient having been treated with antirejection therapy, although biopsy confirmation is becoming more common. In a review of 8777 rejection episodes over a 15-year study, there were, on average, 0.89 rejection episodes for each LD transplant and 1.23 for each DD transplant. A remarkable decrease in the incidence of acute rejection has occurred over the past 20 years (Table 41-3). In a study of two cohorts of pediatric renal transplant recipient (1469 in 1987–89; 1189 in 1997–99), the rejection ratios dropped from 1.6 to 0.7/patient.[131] Sixty percent of the latter group were rejection-free compared to 29% of the former and 1-year graft survival was 94% compared to 80%. Historically, more than half of the patients experienced a rejection in the first posttransplant weeks; now the majority experiences a rejection-free first year.

TABLE 41-3 12-Month Probability (%) of First Rejection, by Transplant Year

TRANSPLANT YEAR	LIVING DONOR		DECEASED DONOR	
	%	SE	%	SE
1987-1990	54.1	1.7	68.7	1.5
1991-1994	44.9	1.5	60.3	1.6
1995-1998	33.1	1.4	40.5	1.7
1999-2002	22.3	1.3	27.2	1.8
2003-2007	8.7	1.3	17.7	1.5

(Adapted from J.M. Smith, D.M. Stablein, R. Munoz, et al., Contributions of the transplant registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], Pediatr. Transplant. 11 [4] [2007] 366-373.)

Risk factors for rejection after DD transplantation include the absence of prophylactic T-cell antibody therapy, donor age younger than 5 years, African American race, and no DR matches. Risk factors for rejection after LD transplantation are the absence of T-cell antibody and one or two Dr mismatches, African American race, and ATN. In an earlier study, the NAPRTCS noted that when reviewed by age groupings, rejection ratios, time to first rejection, and the mean number of rejection episodes were not different; however, for the initial rejection episode, recipients younger than 6 years of age had significantly increased irreversible rejections leading to graft loss.[26] There are conflicting data about whether infants and small children have a "heightened" immune response and an increased incidence of acute

rejection episodes. Indirect evidence suggested a more vigorous immune response especially in infants.[36] Also, data from the UNOS registry demonstrated a higher rate of acute rejections in young children after both LD and DD transplantation, although adolescents were noted to have a higher rate of late acute rejections.[17] On the other hand, data from surveillance transplant biopsies suggest equivalent rejection responses in all groups.[43] Data from one large pediatric transplant program demonstrated that infants have a lower rate of acute rejection than older children.[45] A recent SRTR report demonstrated that infants and young children now have the best outcomes of all age groups.[13] Thus either the proposed heightened immune response has been overcome by improved immunosuppression or the cause of previously poor outcome was related to other factors.

Diagnosis of Acute Rejection

Rejection is suspected when there is decreasing urinary outflow and a rising serum creatinine. In the past, classical signs of acute rejection included fever and graft tenderness. Under CNI and prophylactic antibody therapy, however, these signs are rarely seen; thus early evidence of graft dysfunction should initiate concern. The differential diagnosis consists of ureteral obstruction, renal vascular compromise from stenosis, urinary leak, and an infectious process. When rejection is suspected, a urinalysis and urine culture should be performed to assess the possibility of infection. The urinalysis is also helpful if it suggests intragraft inflammation or immune response as evidenced by proteinuria and the presence of leukocytes and other cells in the sediment. Blood or urinary cytokine analysis may also be useful for diagnosing rejection, although it is not used on a routine clinical basis.[132,133] Examination of the urine sediment may be useful in detecting other reasons for graft dysfunction such as infection or recurrence of the primary kidney disease. An ultrasound is performed to rule out anatomical obstruction. Obstruction can be the result of a lymphocele, hematoma, or rarely, an abscess. The ultrasound can also provide information about intragraft blood flow and pressure.[100] A radionuclide renal scan, using a tracer such as ^{99M}Tc-MAG 3, is a very helpful tool in establishing some diagnoses (see Figures 41-4 through 41-6).[134] Rejection is suggested by rapid uptake of the tracer by the kidney but a delayed excretion. Unfortunately radionuclide scans cannot distinguish among various causes of intragraft dysfunction, such as rejection, cyclosporine toxicity, and ATN. Thus a definitive diagnosis of rejection requires a transplant biopsy.

Pediatric Renal Transplant Biopsy

The renal transplant biopsy procedure is very easy and safe when conscious sedation and ultrasound guidance are used. Recent data evaluating more than 150 pediatric renal transplant biopsies, including some in intraperitoneal kidneys and many performed during the first week posttransplantation, have demonstrated a very low risk of major complications.[101] A major factor in reducing postbiopsy bleeding is the use of a automated biopsy devices using a small (18 gauge) rather than the standard (15 gauge) needle. Biopsies should be performed in pediatric renal transplant recipients whenever the diagnosis of rejection is in doubt.

Treatment of Acute Rejection

Standard treatment of an episode of acute rejection is intravenous methylprednisolone in a single daily dose of 10 to 20 mg/kg (maximum dose: 0.5 g), for three consecutive days. Most grade I and II rejections will respond to steroid therapy. Steroid resistant rejection episodes are treated with T-cell antibody, such as the polyclonal antithymocyte globulin Thymoglobulin. Thymoglobulin is given in a dose of 1.5 to 2 mg/kg /dose for a total of 10 to 14 days. It may be advisable to monitor $CD3^+$ cells during treatment and restrict the frequency of dosing only to days when the count is greater than 20 cells/mm^3.[135] All antibodies have several side effects. Precaution against the potential anaphylactic reaction related to polyclonal antibodies consists of using 500 mg of methylprednisone with the infusion of the antibody and administration of an antihistamine, such as diphenhydramine (Benadryl), 30 minutes hour prior to drug administration.

Reversibility of Acute Rejection

NAPRTCS data observe that among LD kidneys, 55% of rejection episodes were completely reversed, 40% were partially reversed, and 5% end in graft failure. Similar figures for DD kidneys are 48%, 45%, and 7%, respectively.[27] When stratified by age, young transplant recipients more frequently have irreversible rejection episodes. Ten percent of acute rejections among infants receiving a LD kidney ended in graft failure, compared to 4% for older children. For DD kidneys the rate of graft failure in infants was 15%, compared to 7% for older children. Despite decreasing rejection frequency, complete reversal for pediatric LD recipients seems to be improving in later cohort years.[31] Molecular or genomic characterization of rejection biopsies may be helpful in describing different types of acute rejection.[132,133,136–138]

In those patients where neither steroids nor antibody therapy have successfully reversed a rejection episode, conversion to an alternative CNI or to other immunosuppressants may be warranted. There have been no controlled studies in children to document reversal of rejection with conversion to tacrolimus; however, anecdotal reports do suggest that in some cases conversion helps to stabilize graft function.[139–141]

Chronic Allograft Nephropathy

The gradation from acute to chronic rejection is gradual; however, many biopsies may show features of both, and some characteristic vascular changes of chronic rejection may be seen as early as 10 days posttransplantation.[142] The clinical picture is that of gradually declining renal function together with varying degrees of proteinuria and hypertension.[143] The clinical condition may be referred to as transplant glomerulopathy, chronic rejection, chronic allograft dysfunction (CAD), chronic allograft nephropathy (CAN), or interstitial fibrosis and tubular atrophy (IFTA).[144] The succession of names reflects lack of clarity of the etiology, clinical course, or treatment of this disorder. Nonetheless, this process, which will be referred to as CAN in this chapter, is the leading cause of graft loss following kidney transplantation in children (see Table 41-2).

An ongoing controversy exists as to whether the changes seen in chronic rejection are immune mediated, secondary responses to infection, ischemic in nature, or nonimmunological injury due to hyperfiltration.[145–148] Data in children have shown clearly that acute rejection is a predictor of chronic rejection.[34] In a study of 1699 LD and 1795 DD recipients NAPRTCS noted acute rejection was a relative risk (RR) factor for chronic rejection (RR = 3.1), and multiple acute rejections increased the RR to 4.3. Late acute rejections are also clinical correlates of chronic rejection.[149] Even if acute rejection is the most critical element in the genesis of chronic rejection, other immune mechanisms may mediate its progression, such as antibodies directed against the donor, major histocompatibility complex class I-related chain A (MICA), endothelial cells, and B lymphoblasts.[150] Gene expression profiles in graft biopsies of patients with established CAN demonstrate upregulation of profibrotic and growth factors.[151]

Symptomatic therapy is currently the only available method of dealing with CAN. Hypertension should be controlled, and the proteinuria may occasionally respond to angiotensin-converting enzyme (ACE) inhibitors; however, renal function will generally continue to decline. In children, CAN produces an additional burden since decreased renal function will result in deceleration of growth.[152,153] It is in this context that prevention of chronic rejection by early aggressive therapy in patients who have had an episode of acute rejection may be rewarding. Since currently available immunosuppressive medications have been unsuccessful in preventing or slowing the progression of chronic rejection, the use of immunosuppressives other than those currently approved may be reasonable, such as the use of mammalian target of rapamycin (mTOR) inhibitors or costimulation blockade rather than nephrotoxic CNIs.[128,154–158] Although some programs have concluded that these techniques might be beneficial after CAN is established,[159] there may be a point at which substitution of nonnephrotoxic agents is not helpful.[160] The presence of heavy proteinuria in recipients with CAN may also predict lack of benefit of changing chronic immunosuppression.[161]

Recurrent Kidney Disease

Some diseases will recur in a transplanted kidney, and the recurrent disease may lead to loss of the graft, as it had done to the native kidneys previously. Recurrence of the original disease is the cause of 7% of all graft losses (see Table 41-2); and it is the cause of up to 9.5% of graft losses in subsequent transplants.[31] Thus recurrence is one of the top four causes of all graft losses. The 5-year LD graft survival for children with FSGS is 71%, and for children with glomerulonephritis it is 77%, in contrast to all other causes of ESRD in which 5-year graft survival is greater than 83%. In the DD group, 5-year graft survival rates for children with FSGS, glomerulonephritis, and congenital nephrotic syndrome are less than 64%; hemolytic uremic syndrome hemolytic uremic syndrome (HUS) and familial nephritis have rates of 66%; and all other causes have a rate of 70%. Several publications have reviewed the course of recurrent disease in pediatric kidney transplantation.[88,162,163] In some cases, recurrence of some features of the disease without affecting graft survival up to recurrence of the full disease is seen with substantial reduction in graft survival. Unfortunately, there has been very little change in frequency of recurrent disease in pediatric grafts, despite substantial changes in immunosuppression during the past 2 decades.[164]

Focal Segmental Glomerulosclerosis

FSGS is the most common cause of steroid resistant nephrotic syndrome leading to ESRD and is the most common acquired cause of ESRD in children. Reports of recurrence of FSGS vary from 15% to 50% and about 50% of the recurrences lead to graft loss.[162–164] FSGS is a pathological diagnosis and represents the appearance of a large number of diseases that might be due to immunological, genetic, or other causes. The genetic diseases do not seem to recur in a graft. Risk factors for recurrence include early onset of nephrotic syndrome, rapid progression to ESRD (<3 years), resistance to treatment, Caucasian or Asian race, recurrence in a previous transplant, and possible presence of a circulating *glomerular permeability factor*.[102,164] Recurrence can occur immediately after transplantation and result in massive proteinuria, acute tubular necrosis, and even graft failure related to small vessel thrombosis.[102] Typical FSGS lesions on pathological examination, other than foot process fusion, may not appear early in the course of recurrence, but may follow early thereafter. In general, children with active nephrotic syndrome are not candidates for preemptive transplant because of the heavy proteinuria and consequent risk of graft thrombosis and delayed diagnosis of recurrence.[162] Many programs will perform native nephrectomy and will maintain the children on chronic dialysis for some period of time, certainly to improve nutritional status and to normalize the serum albumin. There is no benefit to LD transplantation in children with recurrent FSGS; although graft loss due to rejection is lower in recipients of LD transplants, graft loss due to recurrence is higher, leading to equivalent graft survivals in LD and DD transplants.[102,165] Whether this result is because of a higher frequency of recurrence in LD recipients, a more aggressive course in those recipients or simply a higher rate of rejection in the DD recipients is not known. Plasmapheresis is often used prophylactically prior to transplantation or immediately after it to attempt to prevent or treat recurrence of FSGS,[166–169] and some programs report complete remission in up to 60% treated in that manner. Although no specific immunosuppression protocol has demonstrated clear efficacy in treating or preventing recurrent FSGS, there is some evidence that high dose cyclosporine may be effective in doing so.[168,169] Whether the high dose is needed to counteract the effect of high serum levels of low-density lipoprotein, which binds free cyclosporine, or whether the beneficial effects are due to direct action on podocytes is not clear.[88,170] Rituximab has also been used to treat recurrent FSGS in children, with mixed results.[171–174]

Hemolytic Uremic Syndrome

HUS in children is most commonly caused by enteropathic bacteria, and the disease typically does not cause ESRD or recurrence in a kidney transplant.[175] On the other hand, children with atypical or non-Shiga toxin-associated HUS have a much higher incidence of progression to ESRD and recurrence of the disease after transplantation.[89,176,177] The recurrence is very infrequent after diarrhea-associated HUS, but up to 80% in atypical HUS.[88] Although CNI have

been associated with de novo HUS in a few kidney transplantations, their use in recurrent disease seems to have no effect.[88] In patients with factors H, I or B mutations, the recurrence rate appears to be high and transplantation may be deferred. Some have proposed plasmapheresis with fresh frozen plasma in this setting,[89] and combined kidney-liver transplantation has been proposed for some children with factor H mutations.[89]

Membranoproliferative Glomerulonephritis, Types 1 and 2

Both forms of membranoproliferative glomerulonephritis (MPGN) can recur in transplants, with variable frequency from 30% to 60%.[88] Type 2 seems to be more severe, and neither form seems to be treatable after recurrence.[178]

Oxalosis, Methylmalonic Acidemia and Metabolic Diseases

Primary oxalosis recurs almost immediately and universally after kidney transplantation and was once considered a contraindication to kidney transplantation. However, treatment with intensive pretransplant and posttransplant plasmapheresis to lower the body burden of oxalate, and the use of combined kidney-liver transplantation has led to substantially better outcomes.[179–183] If liver transplantation is being considered, however, careful consideration must be paid to determining whether the child has a variant that might be responsive to lifelong treatment with pyridoxine rather than liver transplantation.[88] Methylmalonic acidemia may be partially ameliorated by kidney transplantation, but full treatment may require liver transplantation in select recipients.[88] Certain inherited diseases including insulin-dependent diabetes mellitus and sickle cell disease may recur in a kidney transplant, but this almost universally happens during adulthood, many years after the primary transplant in a child.

Other Autoimmune Diseases

Immunoglobulin A (IgA) nephropathy, Henoch-Schönlein purpura, lupus nephritis, and antineutrophil cytoplasmic antibody ANCA-associated vasculitis may recur following kidney transplantation in children, but these recurrences may be minimally apparent and less frequently lead to graft loss.[88]

Cystinosis

ESRD is typically the earliest organ failure in children with cystinosis and often accounted for the bulk of deaths from this disorder. However, the use of kidney transplantation and cystine-depleting therapy with cysteamine has extended their life expectancy to the fifth decade.[184–187] Although cystine may accumulate in the interstitium of renal grafts, it does not cause graft failure. However, the unremitting accumulation of cystine results in substantial nonrenal morbidity and mortality.[186,188]

GRAFT SURVIVAL

Pediatric renal centers reporting graft survival show varying results. Because the number of patients at any one center is small, such data cannot represent the pediatric transplant population at large. Furthermore, multiple factors affect graft survival, such as donor and recipient age, histocompatibility matching, recipient race, and so forth. Thus there cannot be accurate descriptions of graft survival rates without classification of the important variables. To obtain a proper population mix representing gender, age, and racial diversity, multicenter registry results such as SRTR and NAPRTCS annual reports have been used.[31,39]

NAPRTCS has recorded that a total of 2556 graft failures occurred between 1987 and 2007, representing about 25% of all transplants in that time frame. Of the failures, about 9% were deaths with a functioning graft, 84% were returned to dialysis, and 7% were retransplanted at the time of failure. Table 41-2 provides the distribution of causes of graft failure. With increased length of follow-up, chronic rejection continues to increase in importance; it is now the most common cause of graft failure. Overall, 48% of graft failures are caused by rejection with chronic rejection accounting for 35% and acute rejection accounting for 13%. Recurrence of original disease as a cause of graft failure was observed 174 times, accounting for 7% of graft failures. The specific diseases include: focal segmental glomerulosclerosis accounted for 44% of these graft losses, membranoproliferative glomerulonephritis type II 9%, HUS 9%, oxalosis 5%, chronic glomerulonephritis 4%, others 28%. Vascular thrombosis remains a major cause of failure, and 361 graft failures (14.1%) were attributed to primary nonfunction, vascular thrombosis, or miscellaneous technical causes. These data show that such problems occur in about 4% of all pediatric transplants.[60,92,112,114,116,117,189] Considering just transplants that have been performed since January 1, 2000, chronic rejection is the leading cause of graft loss (41.3%), followed by vascular thrombosis (8%), recurrent disease (7.9%), acute rejection (6.3%), and medication discontinuation (6.3%).[31]

Overall 5-year graft survival curves by donor source are shown in Figure 41-9. Expected graft survival for index transplants performed in the last decade at 1, 3, 5, and 7 years for LD kidneys is 95%, 91%, 85%, and 79% respectively, and for DD kidneys it is 93%, 84%, 77%, and 65%. There has been a continuous improvement in short- and mid-term graft survival rates, mostly due to marked improvements in early graft survival rates. This may be related to the decreased frequency of acute rejection rates and the decreased incidence of acute rejection as a cause of graft loss. It is notable, however, that, as shown in Figure 41-9, the slopes of the graft survival curves have not changed significantly over the past 2 decades. These important trends in improved graft survival in pediatric LD and DD renal transplantation outcomes have been reported frequently over the past decade,[13,26,31] and the most recent data are shown in Figures 41-2 and 41-9.

Table 41-4 shows relative hazards (RH) for graft failure for selected transplant characteristics for both living and deceased kidneys. Relative risks of graft failure are derived using Cox proportional hazards regression models. For recipients of LD grafts, the most influential prognostic variables of index graft survival are race (African American vs. non-African American; RH=1.95, $P<.001$), prior transplant (RH=1.35, $P=0.006$), lack of induction antibody treatment (RH=1.15, $P=0.035$), and lack of HLA-B matches (RH=1.40, $P=0.008$). A linear trend in improvement of graft survival with more recent year of transplantation has also been observed (RH=0.95 per year, $P<.001$).[31] For DD recipients, the important prognostic factors include: African

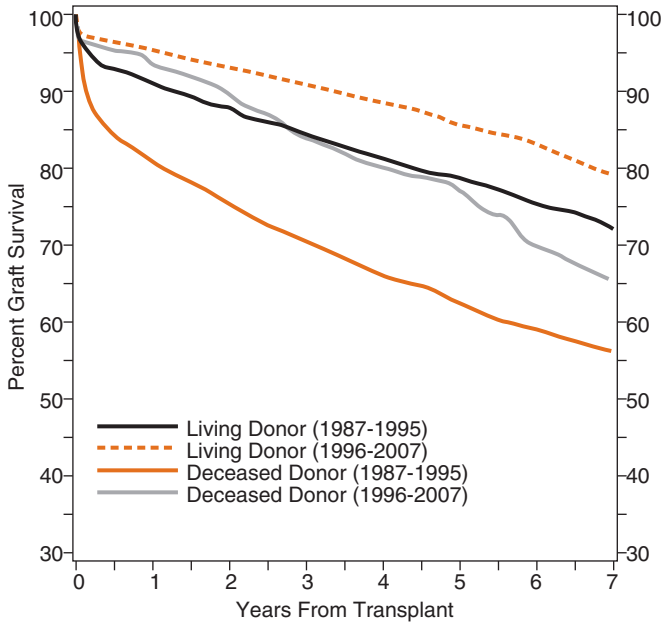


FIGURE 41-9 Five-year actuarial graft survival in children from LD and DD renal transplantation. (Adapted from J.M. Smith, D.M. Stablein, R. Munoz, et al., Contributions of the transplant registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], Pediatr. Transplant. 11 [4] [2007] 366-373.)

TABLE 41-4 Relative Hazard Analysis for Graft Failure in Multivariate Proportional Hazards Model

	LIVING DONOR		DECEASED DONOR	
	RH	P-VALUE	RH	P-VALUE
Recipient Age (>2)	1.16	NS	0.62	<0.001
Prior transplant	1.4	<0.001	1.47	<0.001
Induction antibody	0.83	0.003	0.9	0.080
>5 Lifetime transfusions	1.24	0.010	1.28	<0.001
No HLA-B mismatches	1.39	0.006	1.16	0.013
No HLA-DR mismatches	0.84	NS	1.12	0.060
Black race	1.99	<0.001	1.54	<0.001
Prior dialysis	1.16	0.044	1.21	0.052
Cold storage time >24 hours	-	-	1.15	0.025
Transplant year	0.95	<0.001	0.94	<0.001

(Adapted from J.M. Smith, D.M. Stablein, R. Munoz, et al., Contributions of the transplant registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], Pediatr. Transplant. 11 [4] [2007] 366-373.)

American race (RH=1.56, $P<.001$), prior transplant (RH=1.43, $P<.001$), age older than 2 years (RH=0.59, $P<.001$), and male gender (RH=0.85, $P=0.005$. The same linear trend of improved graft survival rates in later transplant years is also seen (RH=0.94 per year, $P<.001$). A history of prior dialysis may be a slight relative risk (RH=1.23, $P=0.04$). Lack of HLA-B and -DR matches also seem to be relative risks to graft survival in DD transplants, as is prolonged cold-storage time. For both LD and DD transplants, a history of more than five lifetime blood transfusions seems to be associated with worse graft survival rates, but the significance of this finding in the modern era is not clear. Also, the interpretation of the use of induction antibody treatment is hampered by selection factors that motivate its usage; the size and direction of these biases cannot be quantified, and the evaluation of this factor cannot be considered definitive. Importantly, the improvement in graft survival rates in very young recipients is strongest in the LD recipients, and the overall improvement in this age group may be related to the high percent of LDs used for them.

Another measure of long-term graft function is the calculation of graft half-life. An analysis of 8922 pediatric and 78,418 adult renal transplants demonstrated superior long-term graft function in young pediatric recipients (17). Infants (age 0–2 years) had the worst 1-year graft survival rates (71%) compared to children (3–12 years) (83%), adolescents (13–21 years) (85%), and adults (86%). However, for all grafts that survived at least 1 year, infants had the longest projected half-life (18 years), compared to children (11 years), adolescents (7 years), and adults (11 years). A similar analysis of UNOS data showed that young recipients who received adult donor kidneys and had immediate graft function had projected half-lives of greater than 25 years, better even than HLA-identical adult donor-recipient pairs.[61]

While assessment of graft survival is a reasonable measure of transplant outcome, it does not include an accurate portrayal of the course of CAN. The usual course of a kidney transplant includes an inexorable and continuous decline in renal function over many years. Thus many kidney transplant recipients suffer from the consequences of CKD for many years as graft function deteriorates. This decline is shown in Figure 41-9. As noted above, the various causes for decrease in kidney function include immunological, such as immune response or rejection and recurrent disease; and nonimmunological, such as nephrotoxic medications, infection, perfusion injury, and so forth. Studies designed to identify the causes and ameliorate any etiological causes are clearly indicated.

The primary disease causing ESRD can have an effect on graft survival. Children with oxalosis used to have very bad outcomes, to the extent that the diagnosis was considered a contraindication to transplantation. However, improvements in outcome related to combined liver-kidney transplantation have been encouraging[41,104,179–183] after using intensive hemodialysis prior to and immediately after transplantation and performing the procedure before complications of the disease have caused multiple organ damage in the recipient. There have been reports of using the recipient liver in a "domino" procedure as the graft for another patient with liver failure due to other causes. Unfortunately, all of the complications of oxalosis quickly occur in those recipients.[190] Similarly, infants with congenital nephrotic syndrome often had very poor outcomes,[104,184] but strategies designed to reduce the risk of thrombosis and improve nutrition pretransplantation have led to marked improvements.[63–65,115] FSGS can be a devastating disease that may recur very quickly following renal transplantation, sometimes as early as the first posttransplant day.[184,191–194] Although recurrence is no more frequent in LD transplants, the graft survival advantage of LD transplantation is lost for children with FSGS.[165] Little is known about the pathophysiology of the disorder or the cause for recurrence.[195,196] There are several

proposed approaches to preventing or treating recurrence, mostly involving enhanced immunosuppression with plasmapheresis.[88,194,197–202] Lupus nephritis surprisingly does not recur following renal transplantation to any great extent. Patients with lupus have similar outcomes compared to other patients,[203,204] except for a slight increase in mortality,[204] an increase in incidence of recurrent rejections and a slight tendency to graft failure in those patients receiving DD grafts following peritoneal dialysis.[203] Children with sickle cell disease and ESRD can receive kidney transplants successfully,[205] as can those with Down syndrome.[206,207] HUS has been variably described as likely to recur or not.[184,208] After distinguishing the etiological factors, epidemic Shiga toxin-associated hemolytic syndrome is unlikely to recur following renal transplantation,[175,177] whereas atypical or familial HUS may recur with devastating and irreversible consequences.[177]

GROWTH FOLLOWING TRANSPLANTATION

A major distinguishing feature of pediatric from adult recipients is the need for children to grow. The growth failure commonly observed in children at the time of transplantation is multifactorial; however, the most important cause is the reduced response to endogenous growth hormone,[209] related to several mechanisms. Growth failure often begins insidiously early in the course of CKD. In a NAPRTCS analysis of 1768 children with CKD (glomerular filtration rate <75/ml /min/m^2), more than one third had a height deficit of more than 2 S.D.s. It has been amply demonstrated that chronic renal insufficiency beginning in infancy leads to permanent reduction in growth potential.[210] Growth retardation continues in children on a dialysis regimen, whether the mode of dialysis is peritoneal or hemodialysis. For several years, it has been suggested that a functioning transplant would enable the child to achieve catch-up growth.[8] Unfortunately, long-term data from registry studies has shown a more disappointing outcome.

NAPRTCS data shows that the mean height deficit at the time of transplantation is −1.88. Males (−1.92) and younger recipients have greater height deficits at the time of transplantation.[37] Younger children can show catch-up growth[8,211] with complete inversion of Z-score up to 0.6 at 2 years for those younger than 5 years of age at transplant. Older children may grow at a normal rate, but rarely show catch-up growth. The Z-score for 19-year olds is −1.5. Final adult height for children with ESRD is improving, but all of the improvements seem to be related to the gains achieved during treatment for CKD rather than after transplantation.[9] On a positive note, however, there has been an improvement in the height deficit at the time of transplantation: In 1987, children receiving their initial kidney transplant were an average of 2.4 S.D. below average, whereas in the 2003 cohort, the deficit was only 1.5 S.D. below average.[31] As a result, the final adult height of children transplanted more recently is much better than those transplanted years ago. The Z-score for children transplanted 1987 to 1991 who have reached their terminal height was −1.93 as compared to −1.08 for those in the 1997–2001 cohort.

These studies on long-term growth posttransplantation are disappointing; however, they do focus on mechanisms that prevent growth despite a milieu with normal renal function. Individual center studies have adopted a variety of techniques, such as discontinuation of prednisone,[211,212] alternate-day steroid therapy,[213–215] steroid avoidance,[7] or the use of recombinant human growth hormone (rhGH).[216] It has been known for several years that steroids used for immunosuppressive therapy will inhibit growth.[217] It has also been demonstrated that steroids affect growth hormone secretion.[152,218–220] Measurements of pulsatile and pharmacologically stimulated hormone release reveal that steroids play an inhibitory role.[217,221] Conversion of children to alternate-day steroid therapy has shown improvement in growth;[214,215] however, the best catch-up growth is seen in patients completely withdrawn from steroids.[7,140,222] Numerous uncontrolled studies have shown that steroids can be withdrawn from children posttransplantation;[7,140,223] however, until recently, acute rejection tended to occur shortly afterwards in many of these patients,[224] with marked detrimental long-term effects. More recent studies, using different approaches to long-term immunosuppression, have shown much better success with the avoidance or withdrawal of steroids, but the effects of these approaches on long-term growth rates is not yet known.[119,120,124,129] An alternative method of attaining catch-up growth post-transplantation would be the use of growth hormone. RhGH is not approved for use in children posttransplantation; however, numerous uncontrolled studies have shown its ability to accelerate growth in this setting.[225] Several complications of the use of rhGH post transplantation have been suggested,[225–228] but a controlled trial demonstrated that it could be used safely and effectively.[10] Although one report suggested that the pretransplant use of rhGH may be associated with subsequent posttransplant lymphoproliferative disorder (PTLD), its use posttransplantation had no such association.

COMPLICATIONS OF PEDIATRIC RENAL TRANSPLANTATION

There are multiple complications of the transplant surgery and of chronic immunosuppression. These complications tend to diminish the success of kidney transplantation. The complications include multiple types of infections; cardiovascular complications, including hypertension and vascular problems; metabolic abnormalities such as hyperglycemia and dyslipidemias; obesity; growth deficiency; and complications of orthopedic, gastrointestinal, neurological, pulmonary and hematological systems.

Adherence to Chronic Immunosuppression Treatment

Nonadherence is often cited as a cause of long-term graft loss in pediatric renal transplant recipients, especially adolescents.[229] A major reason for nonadherence is thought to be the alteration in appearance that accompanies immunosuppressive medications, including the cushingoid facies and growth retardation

related to long-term daily corticosteroid administration and the hirsutism and gingival hypertrophy associated with cyclosporine. However, the true incidence of nonadherence is unknown. Nonadherence rates of 22%,[230] 43%,[231] and as high as 64% in adolescents[232] have been reported. Some factors, such as young age, adolescence, poor socioeconomic status, and family stress have been associated with increased levels of nonadherence.[230,232–234] Importantly, however, healthcare workers are not able to identify a significant proportion of nonadherent patients.[235] Treatments such as educational programs[231] and family-based therapy[236] have been proposed, but these types of programs have not been universally successful in changing motivation.[229] An alternative proposal for improving nonadherence would be to change the type or frequency of immunosuppressive medications so that the recipients do not have to adhere to rigid schedules, but these proposals are currently only hypotheses.[120,237]

Hospitalization

The median duration of hospitalization at the time of transplantation during the first posttransplant month in the most recent NAPRTCS report was 10 days, with longer stays required for young patients and for recipients of DD transplants.[31] The mean hospital stay fell by 50% between 1987 and 2007. Most children require rehospitalization at least once after the initial discharge after renal transplantation. Fifty percent of LD recipients and 62% of DD recipients are hospitalized during the first 6 posttransplant months. The hospitalization rate falls with increasing time after transplantation, but 16% require at least one hospital stay in the fourth posttransplant year.[27] The most common reason for hospitalization used to be for treatment of rejection. However, a recent analysis supports that treatment of viral and bacterial infections are the next most common reasons for hospitalization.[238] The most common bacterial infection in children 5 years of age is *Clostridium difficile* diarrhea and for those older than 5 years, urinary tract infection.[45] Cytomegalovirus (CMV) appears to be the most common viral infection in older children. Treatment for hypertension is the cause for hospitalization in the first 6 months in 5% to 8% of recipients and falls to about 1% 5 years after transplantation.[27]

Posttransplant Lymphoproliferative Disorder and Malignancy

Although PTLD has been reported as a complication of pediatric organ transplantation for many years,[239] the number of published reports seem to be increasing.[240] It is not clear whether this indicates that the incidence of this potentially lethal complication of immunosuppression is increasing or if it is just more readily recognized. If the incidence is increasing, it may be the unfortunate consequence of "improved" immunosuppression.[241] In a review of UNOS data, the incidence of PTLD following pediatric renal transplantation is clearly increasing, and age of older than 18 years, Caucasian race, and male gender are significant risk factors.[242] Current incidence appears to be 1% to 2% of all pediatric renal transplants.

PTLD often appears within lymph nodes, but it can be extranodal, frequently occurring within the gastrointestinal tract,[243] proximate to or within the graft,[244] or distant from it.[245] Presentation of PTLD within the central nervous system is often devastating and rapidly fatal. PTLD is generally thought to emanate from an Epstein-Barr virus (EBV) infection.[243,246,247] Thus the pretransplant EBV status of the donor and recipient may be an important determinant of the disease and may explain why the disease is more common in children than in adults.[248,249] In several reports, the incidence rate of PTLD for EBV-seronegative recipients was many times higher than for EBV-seropositive recipients,[250–252] and in others, the source was the donor in most of the cases.[253] Concomitant primary infection with CMV may increase the risk of PTLD fivefold.[250] The intensity of immunosuppression may also predispose the child to PTLD.[252,254] Treatment with antilymphocyte antibodies, such as OKT3, as either induction or antirejection therapy, may increase the risk of developing PTLD substantially.[250,251,255] Although it has been reported following both cyclosporine and tacrolimus treatment, programs that have used both drugs have suggested that the incidence was higher in tacrolimus-treated recipients.[241,248,256] However, a recent registry report suggests that neither MMF nor tacrolimus were independent risk factors for PTLD; rather the intensity of immunosuppression was most important.[242]

The diagnosis of PTLD has generally been made on the basis of characteristic pathological findings, and the diagnosis cannot be made without biopsy material. Advances in detection of EBV DNA[257–260] and in the outgrowth of transformed lymphocytes[261,262] have permitted early detection of patients at high risk to develop PTLD. Surveillance of blood and prospective adjustment of immunosuppression has been proposed, but there are no universally accepted standards in this area.[262] Similar tests have been used also to guide treatment,[256] but their absolute value for this function is not established.

The mainstay of treatment of PTLD is the reduction or discontinuation of immunosuppression.[253,264,265] Of interest, in many of these cases, the graft is not rejected despite the marked lowering or discontinuation of immunosuppressive medications. Interferon-alfa and intravenous gammaglobulin,[266,267] ganciclovir,[268] and even chemotherapy have been suggested, but their efficacy has been variable. Prophylaxis of high-risk patients may be useful.[269] Treatment with the monoclonal antibody rituximab has shown promising results.[270–274]

Other Infections

Immunosuppression renders the recipient susceptible to numerous viral and bacterial infections. Infections account for the majority of complications posttransplantation in children and are the principle cause of morbidity. Prophylactic therapy against the more common infections seen in the context of a renal transplantation is employed by most centers.

Cytomegalovirus

CMV is an extremely important cause of infectious complications affecting transplant recipients. Unlike the situation

seen in nonimmunocompromised individuals, CMV infection in renal allograft recipients more often causes serious symptoms. CMV presents as a primary infection in seronegative patients; in seropositive patients the infection is secondary due to reactivation of the patient's own latent virus. Clinically the two types cannot be distinguished, although the former is generally more severe. Because of the high risk to the patient and renal allograft, prophylactic therapy is indicated for all seronegative patients who receive a seropositive kidney and for all patients who receive induction with a T-cell antibody. Prophylaxis can be carried out using either specific antiviral therapy or with high-titer CMV immunoglobulin, or both. The incidence of virologically confirmed CMV-associated syndromes was reduced from 60% in controls to 21% in recipients of CMV immune globulin. CMV immunoglobulin is generally given in the first four months posttransplantation. Both acyclovir[275] and ganciclovir[276] have been shown to be effective as prophylactic therapy; however, the latter should replace the former since the introduction of an oral valganciclovir preparation, which has been shown to be highly efficacious.[277,278] The dose of oral valganciclovir is given by (7×BSA×CrCl) with a maximum of 900 mg once per day. There have been no controlled trials of CMV immunoglobulin versus ganciclovir, so the relative merits and indications of the two preparations are unknown, although the former seems to ameliorate the severity of CMV disease while the latter decreases the frequency.

Pneumocystis Carinii

Because of their defective cellular immunity, transplant patients are susceptible to respiratory infections by opportunistic organisms that are not of concern to normal children. Pneumonia is a common cause of morbidity in children with a renal allograft, and *Pneumocystis carinii* is the most important cause, occurring in about 3% of all renal transplant recipients.[280] Pneumocystis produces a diffuse pneumonia in which shortness of breath and hypoxemia are salient features. If diagnosed quickly it can be treated effectively; however, delay can be fatal, and hence prophylaxis is standard therapy in most centers. The risk is highest in the first month and treatment with trimethoprim-sulfa (Bactrim), in the dose of 10 mg/kg three times per week, should be given during the period of highest risk.

Varicella

Chickenpox is one of the constant worries of both the transplant physician and the patient's family, since exposure in the pediatric age range is extremely high.[45] The rash in an immunocompromised patient may become confluent, bullous, and hemorrhagic. If the disease becomes systemic, the fatality rate can be high.[281] Treatment of varicella in immunocompromised children generally consists of intravenous acyclovir at least until all lesions are crusted.[280,282] Prophylaxis, consisting of the administration of varicella zoster immunoglobulin (VZIG), is carried out routinely in all transplanted seronegative children upon exposure.[280] The administration of varicella vaccine (Varivax) prior to transplantation substantially reduces the frequency and severity of the disease posttransplantation.[283] The use of varicella vaccine posttransplantation has been reported in only a small series,[284] but it is likely safe, although not uniformly successful.

Urinary Tract Infection

Urinary tract infections (UTIs) are extremely common during the first 3 months posttransplantation and may be seen in as many as 50% of patients.[45,285] It appears that beyond the first 3 months, episodes of asymptomatic bacteruria are more common. However, during the first 3 months UTI may be a common source of bacteremia.[286] Chemoprophylaxis, by the administration of Bactrim as described for *P. carinii*, should be provided in the first month in all patients and may be continued up to 1 year in patients whose original disease was urological in origin.

Polyomavirus

Polyoma BK virus infection may be an increasingly important cause of graft dysfunction and graft loss following renal transplantation,[287] but there has been little information about its frequency or severity in children. In one retrospective analysis of 100 pediatric renal transplants, 26 had BK virus detected in urine and five in blood.[288] Those with viremia had elevated serum creatinine and evidence of interstitial nephritis on graft biopsies. Screening of susceptible patients by urine analysis for BK messenger RNA has been proposed,[289] but proper therapeutic treatments in response to rising titers have not been identified.

Hypertension

The incidence of hypertension posttransplant is demonstrated in a NAPRTCS study wherein 70% of patients required antihypertensive medications at 1 month posttransplant; the incidence decreased to 59% at 24 months.[290] Hypertension may be detected more commonly if ambulatory blood pressure monitoring methods are used.[291,292] Hypertension posttransplantation is primarily related to the side effects of drug therapy. The two most widely used immunosuppressives, CNI and prednisone, exacerbate preexisting hypertension. Hypertension has been correlated with multiple complications of transplantation, including reduced graft survival and cardiovascular complications.[293,294]

With dose reduction of prednisone and CNI, almost all hypertensive patients can be managed, though multiple drug regimens may be necessary in some patients. An effective and safe drug to use is a calcium channel blocker, such as nifedipine, which also reduces cyclosporine toxicity.[297,298] Another drug particularly favored in adolescent patients because of concerns of noncompliance is clonidine, which is available in a transdermal patch. Clonidine may induce drowsiness, and sudden withdrawal tends to produce rebound hypertension. In patients who complain of palpitations due to drug-induced reflex tachycardia, prazosin is more effective, because it induces the least amount of tachycardia. Minoxidil, an acute vasodilator, should only be used with severe hypertension and for only a limited duration because it causes hirsutism. Care must be exercised to restrict the use of ACE inhibitors, since converting enzyme inhibition in a single kidney model leads to reduction in the glomerular filtration rate.[299,300]

Hyperlipidemia

Steroids, CNIs, and rapamycin induce hyperlipidemia. A fall in serum cholesterol levels on conversion from cyclosporine to azathioprine has been demonstrated.[301] The mechanism by which CNIs might increase plasma cholesterol is not clarified. The drugs are highly lipophilic, and up to 80% is transported in plasma by binding to lipoproteins, particularly low-density lipoproteins (LDL). It is conceivable that the binding to LDL cholesterol results in impaired clearance of LDL from the circulation via cell-surface receptors.[302] Posttransplantation hyperlipidemia in adults has an adverse effect on cardiovascular morbidity.[303,304] NAPRTCS reviewed posttransplantation patients maintained under a rigid common protocol of immunosuppression and observed that at 1 year posttransplant, they did exhibit significantly elevated levels of plasma cholesterol and very low-density lipoprotein (VLDL) cholesterol compared to normal controls; however, the elevated cholesterol levels (mean 213 mg/dl) were not high enough to require lipid lowering agents.[305] In cases with higher serum lipid levels (cholesterol 250 mg/dl or greater), 3-hydroxy -3 methylglutaryl (HMG) coenzyme (CoA) reductase inhibitors are particularly effective in reducing total cholesterol levels.[306,307] The use of rapamycin may increase the need for lipid-lowering agents in the future.

Posttransplantation Diabetes Mellitus

Hyperglycemia and posttransplant diabetes mellitus in children (PTDM) may be increasing in frequency.[308] Corticosteroid use leads to peripheral insulin insensitivity and hyperglycemia that is relatively insensitive to exogenous insulin. Steroid withdrawal has led to improvements in this condition.[309] A NAPRTCS study described an overall incidence of less than 3% of pediatric renal transplant recipients, with African Americans at higher risk.[310] Tacrolimus use was identified as a significant risk factor, a finding confirmed by reports, some with incidence rates exceeding 50%.[139,308,311–313] Tacrolimus may diminish insulin secretion.[313] Treatment may be aided by reducing or eliminating corticosteroid or CNI doses.[309,315]

LONG-TERM OUTCOMES OF PEDIATRIC RENAL TRANSPLANTATION

Rehabilitation

Organ transplantation typically results in dramatic improvement of all aspects of physical, emotional, and social functioning. Importantly, cognitive skills improve after successful renal transplantation,[12] suggesting stabilization of neurophysiological functioning. Health-related quality of life measures are generally good, especially in older children and adolescents, although all ages reports some problems with usual activities.[316] Interestingly, the perceived emotional status of the children was actually better than controls, especially during and after adolescence.[316]

Long-term survival is generally excellent,[317] and measures of quality of life have demonstrated excellent rehabilitation in long-term survivors.[318,319] More than 90% have rated health as good or excellent, and most did not feel that health interfered with normal functioning. Most of them were full-time students or were employed. The majority was below normal height, and up to a third were dissatisfied with their body appearance. In one report, only a small minority of long-term survivors were married,[320] but in another, 50% were married and half of those had children.[319]

Mortality

Infection is generally the major cause of death, particularly in the first posttransplant years.[37] Other major causes include cancer or malignancy, cardiopulmonary causes and dialysis-related complications. The best patient survival results are found in older pediatric recipients and in recipients of LD transplants.[31,104] Risk factors for excess mortality include young recipient age, graft dysfunction (ATN) at day 30 following transplant, and certain underlying renal diseases (oxalosis, congenital nephrotic syndrome, Drash syndrome).[104] Mortality after 10 years posttransplant seems to be related primarily to cardiovascular causes,[31,317] which may be linked to the hyperlipidemia and hypertension associated with chronic immunosuppression. The mortality rate of children, except for the very youngest, is very low and is much better than what is found in adults. Current 1- and 5-year patient survival rates for pediatric LD kidney transplants are 98% and 96%, and for pediatric DD transplants they are 97% and 93%. Although the survival rates for DD grafts are statistically worse than for LD, they have also improved more dramatically, with 5-year survival rates rising from 91% to 96% over the past 2 decades.[31] Young infants tend to have slightly worse survival than older children, but they have also shown marked improvement over the years. During the 1987 to 1995 era, the 3-year patient survival rates were 90% and 79% for infant LD and DD kidney transplant recipients, respectively; and, for the most recent era, those rates have improved to 95% and 93%.[31]

A full list of references are available at www.expertconsult.com.

Chapter 42

NOVEL DIAGNOSTICS IN TRANSPLANTATION

M. Javeed Ansari, M.D., and Terry B. Strom, M.D.

Despite remarkable advances in the understanding of the pathological basis, diagnosis, and management of allograft rejection, current laboratory tests and risk-assessment strategies fail to detect or predict early subclinical rejection or donor-specific tolerance. There are many recipients who could drastically reduce or discontinue immunosuppression, but these potential candidates cannot be prospectively identified by conventional criteria. Currently, the status of the alloimmune response is indirectly assessed by clinical and pathological evaluation of graft function, and ongoing immunosuppressive therapy is guided by monitoring pharmacological drug levels. Thus, there is no reliable way to assess the status of immune response of the recipient towards the allograft. An ideal monitoring assay for clinical use should be noninvasive, sensitive, specific, and relatively inexpensive. Transplantation tolerance is viewed as a dynamic state, and therefore tolerance assays must be able to measure and monitor prospectively the state of tolerance or its loss over time. There is no single test that allows us to monitor a transplant recipient with respect to these parameters. In the absence of such a test, a panel of assays together may show specific patterns that predict acute or chronic rejection or tolerance. This chapter will review the strategies that are being developed to translate basic immunological research into clinically useful assays. It should be noted that none of the assays described are currently approved by the U.S. Food and Drug Administration (FDA) for use in the United States.

IMMUNE MONITORING ASSAYS

Immune monitoring is a way of measuring functional and molecular correlates of alloreactivity to provide clinically useful information for therapeutic decision-making.[1] Immune monitoring assays can be classified into two major groups based on the donor-antigen (Ag) specificity of the measured response as follows: 1) donor-Ag specific assays, and 2) nondonor-Ag specific assays. Donor-Ag specific assays measure the immune response of the recipient specifically against the donor alloantigens. The donor antigens can be in the form of live (fresh or frozen) cells (usually leukocytes) or synthetic human leukocyte antigen (HLA) peptides. When donor leukocytes are used to stimulate responding peripheral blood mononuclear cells (PBMCs) from the recipient, *direct* alloresponses are measured (see Chapter 31 for a discussion on *direct* and *indirect* alloresponses). On the other hand, when donor-specific HLA peptides are used to stimulate recipient PBMCs, *indirect* alloresponses are measured. Availability of donor cells (for use in direct Ag-presentation assays) over an extended period of time is a limiting factor, which has been addressed to some extent by development of techniques to generate and sustain donor cells for use in monitoring assays in transplantation.[2] Table 42-1 summarizes the immune monitoring assays discussed in this chapter.

Donor-Antigen-Specific Assays

Classic Mixed Lymphocyte Reaction

In the classic mixed lymphocyte reaction (MLR), suspensions of responder T cells are cultured with allogeneic (donor) stimulator cells. The foreign histocompatibility antigens (usually the major histocompatibility complex [MHC] class I or class II molecules (see Chapter 31 for discussion on MHC molecules) expressed on allogeneic stimulator cells serve as the activating stimulus to the responding T lymphocytes. MLR with third-party stimulator cells serves as a control for donor specificity. Proliferation of responding T lymphocytes is assessed by [^{3}]-thymidine uptake measurement with a scintillation counter. [^{3}]-thymidine uptake by stimulator cells is prevented by irradiation or treatment with mitomycin C of the stimulator cells. Since a high number of responding T lymphocytes have direct antigen specificity to alloantigens, there is no need for priming.

Does the MLR assay predict outcomes after transplantation? Reduced antidonor responses by MLR have been demonstrated in kidney transplant recipients without rejection and better graft outcomes in comparison to increased antidonor responses in patients with rejection and poor outcomes.[3] Unfortunately, such results have been difficult to reproduce.[4] While the MLR is a simple, inexpensive assay, true antigen specificity is not easily demonstrated. Also, no distinction is made between direct versus indirect or naïve versus memory T-cell responses; only dividing cells are detected. Nevertheless, the MLR remains an important research assay as a general indicator of T-cell reactivity. Modifications of MLR have been used to demonstrate suppressor function of regulatory cells and, more recently, the donor-specific cytotoxic T lymphocyte precursor assay that has provided better information (see later discussion).

TABLE 42-1 Immune Monitoring Assays

DONOR-AG-SPECIFIC ASSAYS
• Classic MLR
• CFSE-mixed lymphocyte reaction (CFSE-MLR)
• Donor-Ag-specific antibodies (DSA)
• Donor-HLA tetramer analysis
• Intracellular cytokine staining
• ELISPOT assay
• Limiting dilution assay (LDA)
• Trans-vivo DTH assay
NONDONOR-AG-SPECIFIC ASSAYS
• T cell responses to non-specific stimulation
▫ Proliferation—CFSE dilution
▫ Intracellular cytokine staining
▫ ATP generation
• Immunophenotyping of recipient PBMC
▫ Regulatory cells
▫ DC subsets
• Cytokine levels
• Soluble CD30 and CD44
• Soluble HLA-G
• Gene expression patterns
▫ Gene polymorphisms
▫ Microarray analysis
▫ RT-qPCR analysis
• Protein expression patterns

CFSE, carboxyfluorescein succinimidyl ester; *DSA*, donor-specific antibody; *DTH*, delayed type hypersensitivity; *ELISPOT*, enzyme linked immunosorbent spot; *HLA*, human leucocyte antigen; *MLR*, mixed lymphocyte reaction; *PBMC*, peripheral blood mononuclear cells; *RT-qPCR*, reverse transcriptase-quantitative polymerase chain reaction.

Carboxyfluorescein Succinimidyl Ester-Mixed Lymphocyte Reaction

To address the issue of which cells proliferate in the MLR, the carboxyfluorescein succinimidyl ester (CFSE)-MLR was developed. In this assay, the responder (recipient) cells are labeled with CFSE that irreversibly binds to intracellular and cell-surface proteins and is subsequently distributed equally between daughter cells on cell division. As a result, halving of cellular fluorescence intensity marks each successive generation in a population of proliferating cells and can be readily followed by flow cytometry (Figure 42-1). Therefore this assay offers

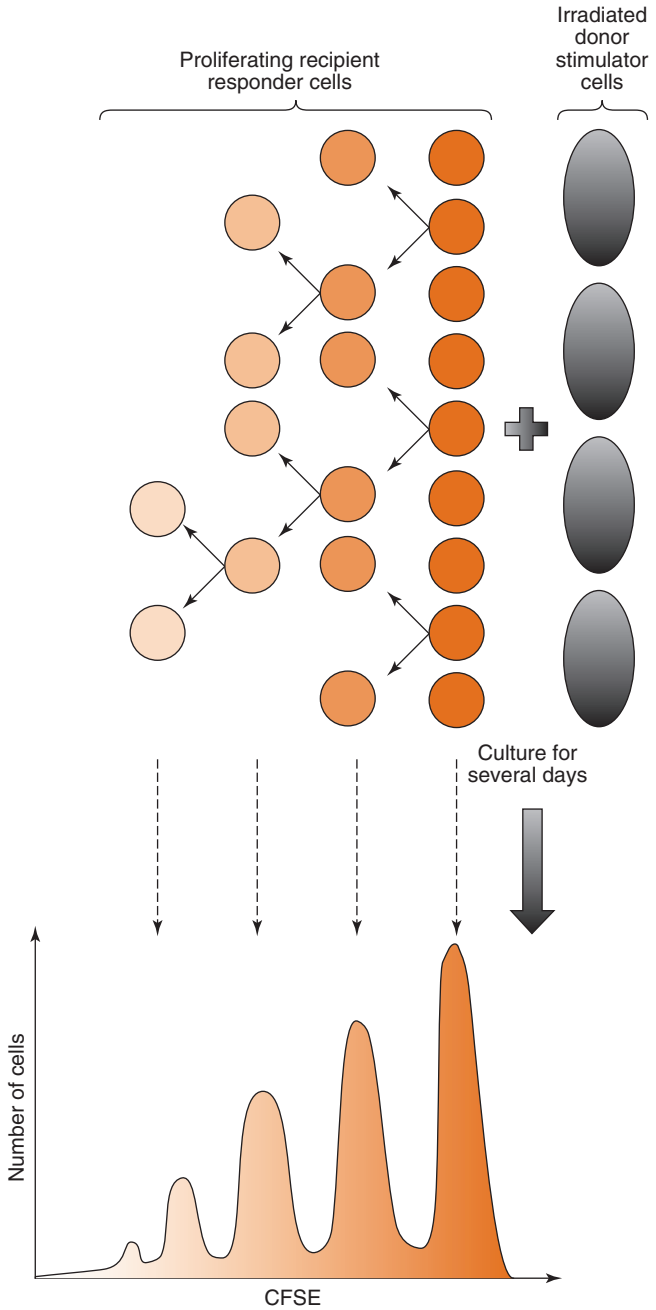


FIGURE 42-1 Schematic representation of CFSE-MLR. CFSE-labeled recipient responder cells are cultured with irradiated donor stimulator cells. Several days later, the cultured cells are analyzed using a flow cytometer and responder precursor frequencies can be calculated.

several advantages, including the avoidance of radioisotopes, the ability to determine whether all cells undergo a few divisions or some cells undergo many divisions, the ability to characterize the dividing cells by immunophenotyping and flow cytometry, and the ability to recover viable cells from the CFSE-MLR by flow-sorting for use in further functional assays or as a source of RNA/DNA for further analysis.

CFSE-MLR has been used widely to assess antidonor responses in experimental, murine systems.[5] Several studies have used the CFSE-MLR assay in humans to assess antidonor responses. For example, in one study of liver transplant recipients, $CD8^+CD25^+$ T cell proliferation in CFSE-MLR was used to distinguish between rejection and graft dysfunction due to other causes;[6] another report in renal transplant recipients compared antidonor responses in campath-treated versus anti-CD25-treated recipients where no difference in proliferative response to donor antigen was seen between the groups.[7] Nonetheless, CFSE-MLR remains a valuable technique, because it can be used to assess suppressor function of regulatory cells (see later discussion).

Intracellular Cytokine Staining

Intracellular cytokine staining is a versatile technique used to analyze cytokine production in individual cells by flow cytometry. The recipient cells are analyzed ex vivo after isolation from the peripheral blood following either nonspecific stimulation or donor-specific stimulation. A transport inhibitor such as brefeldin A is used for a period of time to block the secretion of the produced cytokines, thus permitting detection. Such stimulated cells are first immunostained with fluorochrome labeled monoclonal antibodies (mAbs) targeting surface markers, then fixed and made permeable followed by immunostaining with fluorochrome labeled anticytokine mAbs, and finally analyzed by flow cytometry. Multiparameter staining permits simultaneous examination of multiple cytokines or surface phenotypic markers, or both, to characterize the cell populations producing various cytokines (Figure 42-2).[8] One drawback of the assay is the low signal-to-noise ratio. Fixation increases the hydrophobicity of cellular proteins, thereby increasing their nonspecific binding; therefore it is important to include specificity controls to ensure a higher signal-to-noise ratio.

While there have been many studies in rodent transplantation models using this technique,[9,10] to date there are very few in human transplantation.[11] In lung transplant recipients, intracellular cytokine staining was noted to be more sensitive than limiting dilution assay for detecting interferon-gamma (IFNγ) producing CD8 T-cells.[12] Further, acute lung allograft rejection has been associated with decreased intracellular T-cell transforming growth factor β (TGFβ) in blood and increased intracellular IFNγ and tumor necrosis factor α (TNFα) in bronchoalveolar lavage $CD4^+$ and $CD8^+$ T-cells.[13] Another study in kidney transplant recipients demonstrated that the percentage of IFNγ producing T-helper cells is significantly increased above the pretransplant levels in patients experiencing acute rejection.[14] However, there was no difference in cytokine-producing PBMCs in renal transplant recipients with good graft function compared to those with a diagnosis of chronic allograft dysfunction.[15] More studies are needed to evaluate the use of this technique in monitoring the cytokine production by immune cells as a part of immune monitoring in organ transplantation.

Enzyme-Linked Immunosorbent Spot Assay

The enzyme-linked immunosorbent spot (ELISPOT) assay is a hybrid assay that combines the features of an MLR and an enzyme-linked immunosorbent assay (ELISA) in that the responder (recipient) T-cells are cultured with irradiated donor cells in a polyvinylidene difluoride (PVDF)-membrane backed tissue culture plate, coated with a "capture" (or primary) antibody specific for the cytokine of interest. After a short incubation time (24–48 hours) the cells are removed and a detection (or secondary) antibody is used with reagents similar to a sandwich ELISA. The bound cytokine is detected as a spot corresponding to the cell that produced the cytokine (Figure 42-3). The spots

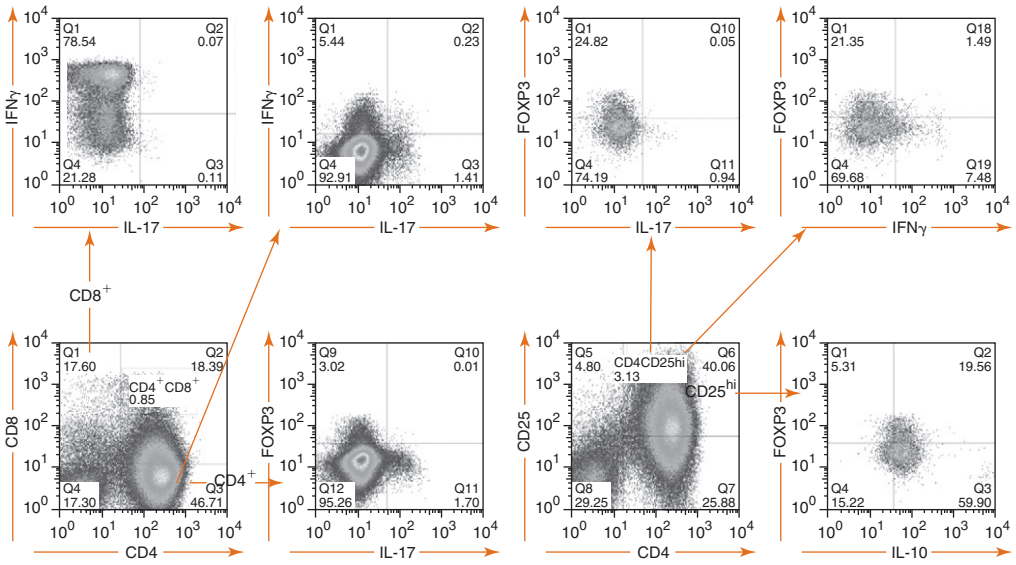


FIGURE 42-2 Dot-plot analysis of multi-parameter flow cytometry data following intracellular cytokine staining. Multi-parameter staining of CFSE labeled cells for CD4, CD25, FOXP3, interferon-[γ] (IFN-[γ]), interleukin-10 (IL-10), IL-17, and dead cell marker 9 days after a mixed lymphocyte culture was performed and analyzed by flow cytometry, illustrating the large amount of information that can be obtained by such assays.

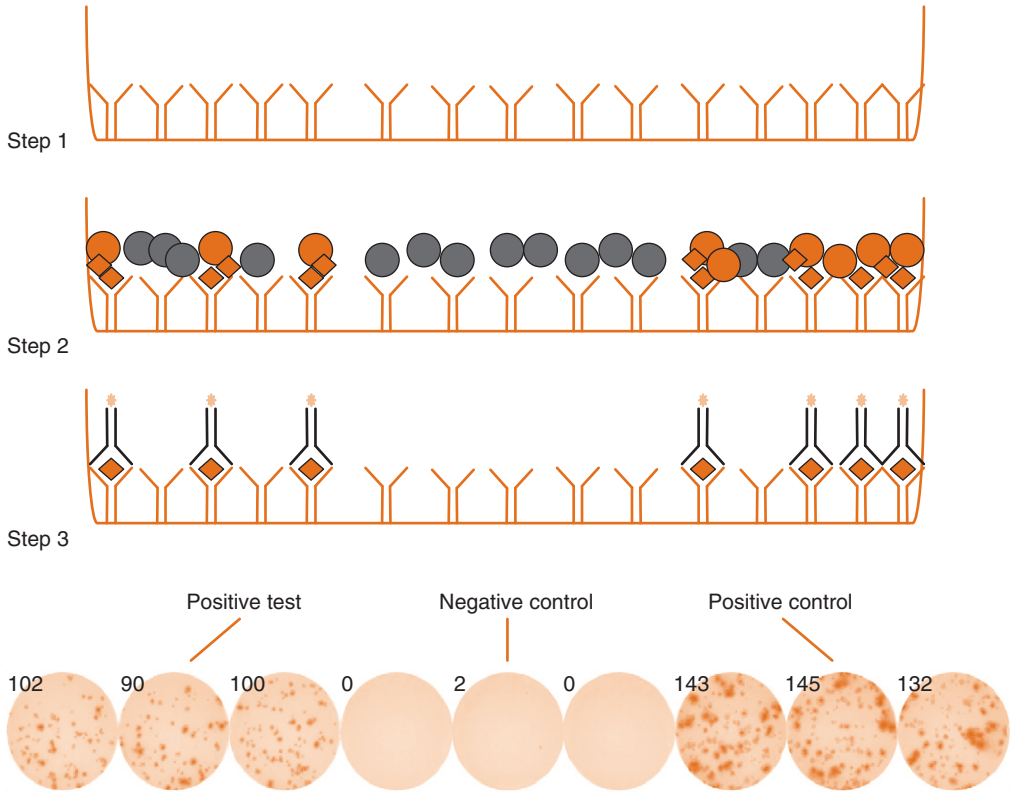


FIGURE 42-3 Schematic representation of ELISPOT assay. Step 1: PVDF membrane is coated with primary anticytokine capture antibody. Step 2: Recipient cells are incubated for 24 to 48 hours and the secreted cytokine is captured by the coated anticytokine antibody. Step 3: The cells are washed away, a secondary anticytokine detection antibody is used to detect captured cytokine by the primary capture antibody, and resulting spots are counted using an ELISPOT analyzer. The appearances of positive test results and negative and positive controls are shown at the bottom of the figure.

are counted with an automated ELISPOT reader system or manually, using a stereomicroscope. Although many cytokines including interleukin (IL)-4, IL-5, IL-10, IL-12, IL-13, and IL-17 can be assayed, IFNγ has been studied the most.

In renal transplant recipients, a significantly higher number of donor-specific IFNγ-producing cells have been found in patients with rejection, as determined by ELISPOT analysis. Furthermore, a trend towards a higher number of IL-10-producing cells was found in patients with stable graft function. The ratio of IFNγ/IL-10-producing cells appeared to be the best discriminator between recipients undergoing a rejection or not.[16] Posttransplant monitoring of alloreactivity by IFNγ ELISPOT assay revealed an independent correlation between early cellular alloreactivity and long-term allograft function.[17,18] In a study that monitored serial IFNγ spots, clinical outcomes were better among recipients with lower frequencies of pretransplantation and posttransplantation IFNγ spots, and significant increases in the number of IFNγ spots preceded the onset of acute rejection.[19] Furthermore, the IFNγ spots decreased after intravenous (IV) steroid administration.[19] Thus an analysis of ELISPOT donor-reactive cells during the early posttransplant period might allow identification of patients at risk for immune-mediated graft deterioration. Further, pretransplant ELISPOT assay might be useful to identify T-cell presensitized patients, who are at heightened risk for severe early acute rejection.[18] Furthermore, recipients with pretransplant donor-specific alloreactivity measured by IFNγ ELISPOT benefited from induction therapy compared to those who did not receive induction therapy.[20] Attempts have been made to assess pretransplant T cell reactivity against a panel of allogeneic cells from cell-banks, termed the panel reactive memory T-cell (PRT) assay, in a manner analogous to panel reactive antibody (PRA) assay (see Chapter 31 for a discussion on PRA) and correlate the results with graft outcome.[21,22] If confirmed prospectively, pretransplant ELISPOT assessments could be used to guide decision-making regarding induction therapy. Another advantage of this assay is that distinction can be made between *direct* and *indirect* alloreactivity. With IFNγ ELISPOT analysis, *direct* antidonor alloreactivity correlated with graft function and *indirect* antidonor alloreactivity correlated with proteinuria in longstanding renal transplant recipients.[23] The Granzyme B ELISPOT assay has also been used as an alternative to cytotoxic T lymphocyte precursor frequency assay (see later discussion) with mixed results.[24,25]

Limiting Dilution Assay

Early attempts at characterizing alloreactivity focused on T-cell proliferation in MLR met with limited success.[26] The classical cytotoxic T lymphocyte (CTL) assay only tests CD8 T-cell function by quantifying the cytolytic activity of recipient T-cells primed in vivo after transplantation. An improved MLR-based limiting dilution assay (LDA), estimating the precursor frequencies of cytotoxic T lymphocytes and helper T-cells provides better information, in that different effector functions can be

measured at different time-points. These include proliferation and cytokine production.

High cytotoxic T lymphocyte precursor frequencies have been associated with prolonged leukemia-free survival time in bone marrow transplant recipients.[27,28] However, the benefit of such an assay in solid organ transplantation has been debated.[4,29] Recently, a Dutch group has studied the use of CTL assay in prospectively identifying living donor kidney transplant recipients for reduction of immunosuppression[30] and reported that 50 of 81 recipients of living donor (LD) kidney transplants displayed third-party, but not antidonor, cytotoxic T-cell responses. Immunosuppression was reduced in each of these patients with only one going on to develop rejection on follow-up. This assay, however, is somewhat cumbersome to perform, requires in vitro non-specific restimulation of cells and generally involves use of radio-isotopes, and the data is complex to analyze, thus limiting its appeal for general applicability (Figure 42-4).

Donor-Human Leukocyte Antigen Tetramer Analysis

This assay involves use of donor antigen specific tetramers that consist of four MHC-peptide complexes linked covalently to a fluorochrome. The tetramers bind specifically to the T-cell receptor (TCR) of T-cells restricted to the donor-specific antigen represented by the peptide present in the tetramer complex. Thus alloreactive T-cells labeled with the tetramers can be quantified by flow cytometry. This technology has been used in autoimmune and viral diseases where, unlike transplantation, the antigenic spectrum is limited and well-defined.[31] Nevertheless, MHC tetramer analysis has been useful in transplantation in situations where alloreactivity against a specific donor antigen is identified. For example, in HLA-matched, minor histocompatibility antigen (HA-1)-mismatched kidney transplant recipients who demonstrated regulated delayed-type hypersensitivity (DTH) response to HA-1 peptide (in the trans vivo DTH assay described later), HA-1-specific HLA class-I tetramer staining identified regulatory and effector CD8 T cell populations.[32] For wider application of this technique, however, the availability of a wide array of MHC tetramers and subsequent validation in multicenter studies is required.

Trans-Vivo Delayed-Type Hypersensitivity Assay

The DTH reaction is a frequent accompaniment of the normal, protective cell-mediated immunity against microbes, for example, the purified protein derivative skin test for immunity to *Mycobacterium tuberculosis*. The DTH is mediated by T-cell-dependent, macrophage activation leading to inflammation and tissue injury. Acute rejection is generally considered to be a manifestation of cell-mediated immunity to graft alloantigens and shares many of the pathophysiologic features of DTH, such as intense lymphocytic infiltration, edema and tissue necrosis.

In transplantation research, the DTH is commonly assayed to quantitate cell-mediated immune reactions. Skin testing for donor-reactive DTH responses would be a reasonable method for monitoring T-cell allosensitization, but repetitive subcutaneous injection of donor antigens in a

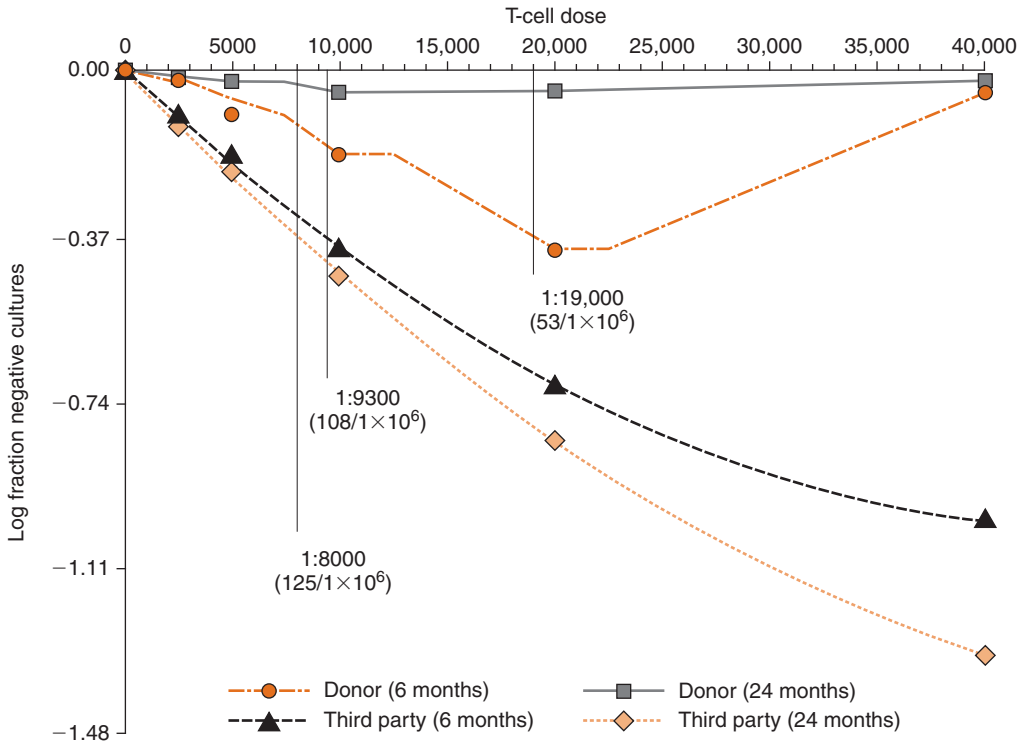


FIGURE 42-4 CTL-precursor frequencies in donor bone marrow cell infused LRD-kidney recipient at different time points posttransplantation: Limiting dilution analyses performed with recipient PBMC at indicated time points against irradiated PBMC from the donor or third party stimulators. Data indicates that, at 6 months posttransplantation, 53 of 1 × 10^6 recipient T-cells were reactive to the donor; the disappearance of CTL at higher T-cell doses indicated the presence of regulatory cells in the recipient's responding PBMC. The donor specific CTL-precursors disappeared from the peripheral blood at 24 months posttransplantation. (Courtesy Dr. James Mathew, Northwestern University, Chicago, IL.)

transplant recipient may promote allosensitization. Therefore, the trans-vivo DTH assay was developed as an alternative.[33,34] Here, recipient T-cells are injected into the footpads of naïve immunodeficient severe combined immunodeficiency (SCID) mice with donor antigen in the form of whole cells, donor cell lysates or donor HLA-peptide plus self antigen-presenting cells. As controls, saline, third-party cells, and recall antigens such as tetanus or Epstein-Barr virus are injected into different footpads. DTH responses are quantified 24 hours later by measuring the footpad swelling that occurs when primed T-cells encounter the appropriate antigen. DTH response requires presensitization; therefore, unlike a MLR, it exclusively measures memory T-cell responses. A positive DTH response, indicated by footpad swelling in response to donor antigen, suggests allosensitization; while a negative DTH response, indicated by no footpad swelling, may suggest regulation or deletional tolerance (see Chapter 43).

There may also be bystander suppression of responses against recall antigens as a result of linked suppression by regulatory cells. Thus, the trans-vivo DTH assay may be used to divide transplant recipients into three categories: regulators, nonregulators, and sensitized phenotypes (Figure 42-5). An advantage of this assay over the ELISPOT assay is that the mechanism of regulation can be uncovered and a distinction between deletional and regulatory T-cell tolerance can be made by restoring the DTH response in the later situation with the injection of neutralizing antibodies to potential regulatory cytokines such as IL-10 or TGFβ.[33,34]

A study of three functionally tolerant transplant recipients demonstrated that all had intact DTH responses to third-party stimulation but absent DTH responses to donor antigens. The absent antidonor responses were restored by the injection of neutralizing antibodies to IL-10 or TGFβ, suggesting the presence of active regulatory mechanisms. Furthermore, when donor and recall antigens were colocalized, the recall response in these three patients was inhibited, indicating bystander suppression.[34] In contrast, a patient who previously demonstrated operational tolerance and an absent DTH response later displayed a strong DTH response upon experiencing an acute rejection of the transplant. Subsequent studies of the DTH assay in nonhuman primates demonstrated a similar "regulator" response after developing tolerance to kidney transplants.[35] Further, a regulated antidonor DTH response was more common in DR-matched recipients with good graft function while on immunosuppression in a cohort of patients with kidney transplants.[36] These data suggest that trans-vivo DTH assay could potentially be used to guide immunosuppression minimization or even withdrawal. However, another study using this assay failed to show any correlation with outcome or humoral sensitization after kidney or pancreas transplantation.[37] This may be due to the use of different methods in performing this assay by these two groups. Additional studies by different groups are required to determine the general applicability of this assay for immune monitoring in clinical transplantation.

As extension of the trans-vivo DTH assay, humanized mouse models are being developed to study alloimmune responses in vivo.[38,39] These models will probably serve as an important tool in detecting tolerance and assessing donor-specific alloimmune response of recipient cells.

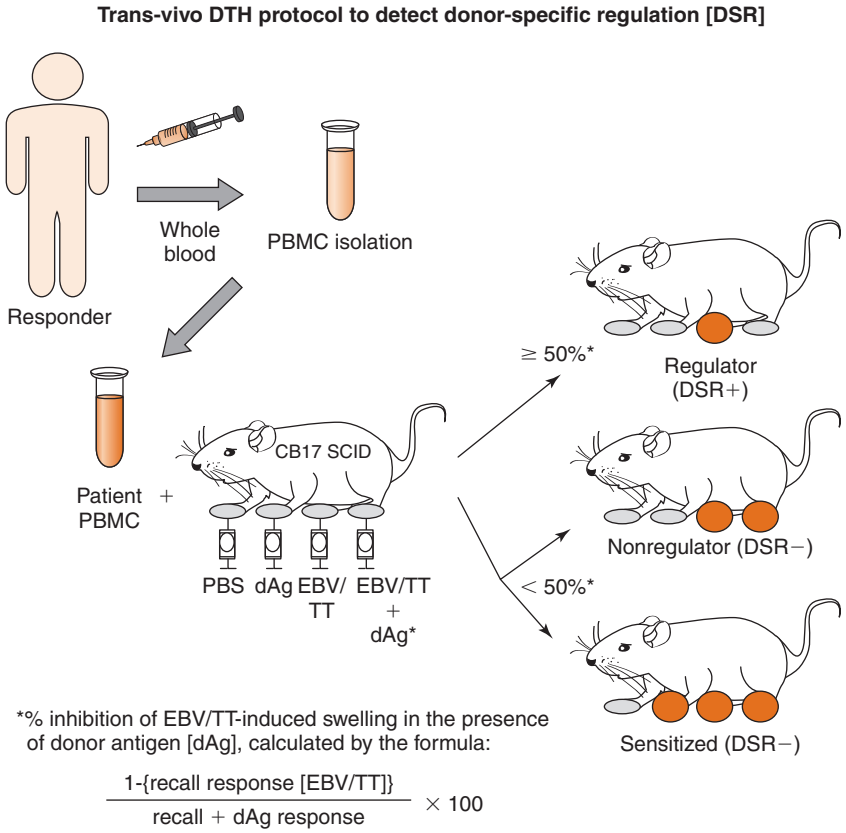


FIGURE 42-5 Schematic representation of the trans-vivo DTH assay: PBMCs isolated from transplant recipient along with donor Ag, EBV/TT, EBV/TT+dAg, or PBS are injected into different footpads of SCID mouse. DTH response is measured by evaluating the footpads 24 hours later for the degree of swelling. Three possible outcomes shown in the figure indicate a regulator, nonregulator, or sensitized phenotype. (Courtesy Dr. William Burlingham, University of Wisconsin, Madison, WI.).

Nondonor-Antigen-Specific Assays

Nondonor-Ag-specific assays have been developed because donor-Ag is either unavailable or the assay may be impracticable. In contrast to the donor-Ag-specific assays discussed earlier, nondonor-Ag-specific assays measure various parameters either directly ex vivo without any stimulation or after nonspecific polyclonal stimulation.

T-Cell Responses to Nonspecific Stimulation

T-cell responses, in terms of cytokine production and T-helper differentiation, either directly ex vivo or after a brief period of nonspecific stimulation, can be assessed as discussed in Intracellular Cytokine Staining earlier or Cytometric Bead Array Assay as discussed later.

Immunophenotyping of Peripheral Blood Mononuclear Cells

Using multicolor flow cytometry, PBMCs may be phenotyped either ex vivo or after a brief period of stimulation (Ag-specific or nonspecific polyclonal). This is a well-established and versatile technique that can be performed in any laboratory with flow cytometry equipment. Thus, a variety of CD markers, chemokine receptors, and intracellular cytokines may be measured, leading to a large amount of information about the prevalent cell types and their frequency (see Figure 42-2). The cells that are relevant to immune monitoring of a transplant recipient are regulatory cells, memory T cells and dendritic cell subtypes.

Regulatory and Effector-Memory Cells

It is widely accepted that regulatory T-cells (T) play a pivotal role in transplantation tolerance.[40] Monitoring of circulating T in the peripheral blood of transplant recipients may be helpful in evaluating the alloimmune status and predict outcome with respect to rejection (either acute or chronic) or tolerance. Different types of regulatory cells have been described.[41] $CD4^+CD25^{high}FOXP3^+$ natural T are the most studied, while other regulatory cells include Th3, Tr1, $CD3^+CD4^-CD8^-$, $CD8^+D28^-$, and $NK1.1^+$ T-cells. Decreased circulating T ($CD4^+CD25^+$ or $CD4^+CD25^{hi}FOXP3^+$) numbers have been noted in liver transplant recipients undergoing acute rejection.[42,43] A low frequency of T is associated with subclinical acute rejection of kidney transplants during the early posttransplant period.[44] On the other hand, increased $CD4^+CD25^+D69^+$ cells have been reported in kidney transplant recipients with stable long-term allograft function.[45] Patients undergoing chronic rejection, however, have lower levels of $CD4^+CD25^+$ cells and *FOXP3* mRNA in blood. Therefore, in this situation the absence of *FOXP3* may indicate chronic rejection.[46] There are conflicting data regarding the significance of $CD8^+CD28^-$ T-cells in the alloimmune response and the use of monitoring these cells posttransplantation.[47–50] However, in a immunosuppression minimization study, stable kidney transplant recipients with circulating $CD8^+CD28^-$ T- "suppressor" cells (Ts) had no acute rejection on follow-up postminimization, compared to 15% rejection rate in recipients with no T prior to immunosuppression minimization.[51] Further, in a CNI-discontinuation study, higher ratios of memory T-cells ($CD8^+CD45RO^+$ or $CD4^+CD45RO^+$ to T ($CD4^+CD25^+FOXP3^+$ were noted immediately prior to discontinuation of tacrolimus in recipients who went on to experience acute rejection compared to those who had stable allograft function.[52] These data indicate the relevance of immune monitoring by immunophenotyping for regulatory cells and memory T-cells in immunosuppression minimization trials.

CD69, a member of the lectin family, is an early marker of T-cell activation, and its expression on CD4 and CD8 T-cells is strongly associated with rejection in pediatric heart transplant recipients.[53] However, in renal transplant recipients only $CD8^+D69^+$ T-cells correlated with acute rejection.[54]

Flow cytometric analysis of urinary sediment predicted the requirement of antilymphocyte therapy and irreversible graft injury in kidney transplant recipients undergoing rejection.[55] Analysis of immune activation markers by flow cytometry and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of urinary sediment was found to be equally useful for monitoring kidney transplant recipients.[56]

Dendritic Cells

Dendritic cells (DC) are professional antigen presenting cells (APC) that play a critical role in the induction and regulation of the alloimmune response. In human peripheral blood, at least two DC subsets have been identified: the $CD11c^+CD123^{low}$ myeloid DC (mDC) and the $CD11c^-CD123^{high}$ plasmacytoid DC (pDC).[57] Measuring the pDC: mDC ratio in the peripheral blood of liver transplant recipients has been used to detect tolerance for prospective withdrawal of immunosuppresion.[58,59] No such studies have been performed in kidney transplant recipients presumably because operational tolerance is much rarer and more difficult to achieve after kidney transplantation compared to liver transplantation.

Cytometric Bead Array (Luminex) Assay

The cytometric bead array (CBA) assay is based on polystyrene particles (microspheres) that are internally labeled with varying amounts of two different fluorophores. When excited by a 635-nm laser, the fluorophores emit light at different wavelengths, 658 and 712 nm. Based on the varying 658-nm/712-nm emission ratios, these beads can be individually classified by a Luminex analyzer. A third fluorophore coupled to a reporter molecule allows for quantification of the interaction that has occurred on the microsphere surface.[60] In the case of cytokine-CBA, the assay uses the principles of sandwich ELISA. The internally-labeled microspheres serve as the solid phase for the sandwich assay and are coupled with anticytokine mAbs, which serve as the capture Abs. The soluble sample is then incubated with the beads and detected with a second (detection) mAb, which is either directly conjugated to a third fluorophore or biotinylated and probed with streptavidin-fluorophore using a flow cytometer. The fluorescence intensity of the detection reagent is proportional to the cytokine being measured. Separately established calibration curves are used to determine the concentration of each cytokine in the test sample, using a dedicated CBA analysis software. Since the internally-

labeled microspheres are differentially labeled with a unique array of fluorophores, multiple bead-sets (multiplex) can be used to detect several analytes (antigens-cytokines, chemokines, etc.) in a single sample at the same time in one assay. This is a big advantage for clinical studies where the sample is often limited. Additionally, multiple independent measurements within each bead population assure good precision. This is a relatively new technology, and while there have been a number of studies that have used CBA assay for cytokine/chemokine analysis in experimental transplantation,[61,62] few human studies have been reported to date.[63,64]

Adenosine Triphosphate-Based Assay for T-cell Activation: The ImmuKnow Assay

The ImmuKnow assay (Cylex Columbia, MD) is based on the principle that intracellular ATP generation correlates with cell activation and proliferation. Although widely available and heavily advertised, the assay is not approved by the FDA within the United States for use in human transplantation. The assay measures an early response to mitogen stimulation (phytohemagglutinin-PHA) by detecting intracellular ATP synthesis in CD4 cells selected from blood by mAb-coated magnetic particles. The ATP is measured by a firefly luciferase luminescence-based assay. The amount of ATP present in the selected cells is a measure of lymphocyte activity.[65] In a retrospective study of tacrolimus tapering in small bowel transplant recipients, it was noted that stable recipients had low immune function compared to those who had rejection and required escalation of immunosuppression.[66] However, this assay is not predictive of acute rejection or significant infections in pediatric heart transplant patients.[67] In kidney transplant recipients with infectious complications, low ImmuKnow levels were noted.[68] Hispanic kidney transplant recipients with moderate or high pretransplant ATP levels had more rejection episodes, particularly in those with an increase in ATP level 2 weeks posttransplant, while patients with ATP levels in the low immune response range had more infections.[69] In a metaanalysis of 504 solid organ transplant recipients from 10 U.S. centers, it was reported that a recipient with an immune response value of 25 ng/ml ATP was 12 times more likely to develop an infection than a recipient with a stronger immune response. Similarly, a recipient with an immune response of 700 ng/ml ATP was 30 times more likely to develop a cellular rejection than a recipient with a lower immune response value.[70] ImmuKnow assay levels were lower in infected lung transplant recipients compared to noninfected recipients and increased with treatment of these infections. It is unclear whether the ImmuKnow assay reflects overimmunosuppressed individuals at risk of infection or bone marrow suppression by infectious agents.[71] Further, ImmuKnow results need to be interpreted to caution in patients receiving Thymoglobulin induction therapy, because higher ATP values were noted despite lower CD4 counts, and ATP values failed to correlate with rejection.[72]

T-Cell Receptor Repertoire Analysis: Tc Landscape

The T-cell receptor repertoire analysis-Tc Landscape assay is based on the observation that the pattern of *Vβ*-gene usage in the TCR during an alloimmune response is very different from that seen in a naive individual. The *Vβ*-gene usage is skewed and restricted to a small number of *Vβ*-genes in a individual experiencing an acute rejection; similarly, the CDR3 lengths also changed to a much more restricted pattern.[73] On the other hand, it is noted that tolerant recipients exhibit high TCR transcript accumulation in a T-cell population with altered *Vβ*-gene/CDR3-lengths.[74] Combining these two variables with the amount of mRNA encoding the TCR using a given *Vβ*-gene/CDR3-length, a landscape is created—Tc Landscape—where the *x* axis represents the *Vβ* chain, the *y* axis represents the CDR3-length, and the *z* axis indicates the amount of mRNA encoding the TCR. All of the studies with this assay have been performed by a French group that originally described this technology. More clinical studies are needed before this assay can be used for immune monitoring of transplant recipients.

GENOMICS IN TRANSPLANTATION

Genomics is the study of the entire DNA sequence of an organism. With the completion of the Human Genome Project and the HapMap Project, several regions of genetic variability between individuals due to single nucleotide polymorphisms (SNPs) or microsatellite polymorphisms have been identified. Multiple studies have shown associations between polymorphisms in candidate genes and transplant outcomes such as acute rejection, delayed graft function (DGF), and chronic allograft dysfunction. With respect to transplantation, a majority of the genes affected by SNPs are immune genes. For example, SNPs in the promoter regions, signal sequences, and introns of a cytokine gene can result in low, intermediate, or high producer phenotype in a particular individual.[75–77] Recipient IFN-γ gene SNPs have been associated with acute rejection, particularly in the presence of MHC class II (HLA-DR) mismatching,[78] and interestingly donor IFN-γ polymorphism is associated with chronic rejection.[79] Toll-like receptors (TLR) are a type of pattern recognition receptors that recognize molecules expressed by pathogens. For example, lipopolysaccharide (LPS), found on the membrane of gram-negative bacteria, mediates activation of the innate immune system via TLR-4. TLR-4 polymorphisms have been shown to mediate differential innate immune activation, which in turn initiates the adaptive immune responses leading to rejection or acceptance in clinical organ and cellular transplantation.[80–82] Killer-cell immunoglobulinlike receptors (KIRs), found on natural killer (NK) cells, interact with MHC-I molecules and regulate the killing function of NK cells. KIR gene polymorphisms may have significant effect on allograft outcomes.[83] Costimulatory polymorphisms such as those of CD28, CD86, CTLA-4, and so on, have also been correlated with clinical allograft immunity.[84–86] Table 42-2 summarizes the studies of SNPs affecting transplant outcomes.

Gene Microarrays

Microarray technology is a powerful tool that has revolutionized the field of genomic research, advancing our knowledge of human health, disease, and pathology. Ever since the first microarray experiment reported in 1995,[87] there

TABLE 42-2 Selected Gene Polymorphisms Affecting Kidney Transplant Outcomes

SNP	ASSOCIATION	COMMENTS	REFERENCES
IFN-γ	Acute rejection, particularly when DR mismatched; donor SNP associated with chronic rejection	IFN-γ is a proinflammatory cytokine, but studies have yielded inconsistent results, perhaps because IFN-γ also plays a role in regulating immunity.	78,79,106,107
TNF-α	Acute rejection; steroid resistant rejection when TNF-α and IL-10 SNPs are inherited together	TNF-α acts in concert with IFN-γ and stimulates an inflammatory response, including neutrophil and macrophage function and augments DTH response. However, inconsistent results have been noted in different studies.	78,107–110
IL-10	Acute rejection	Inconsistent results, perhaps because IL-10 has both proinflammatory and antiinflammatory properties.	78,107–111
IL-6	Better 3-yr graft survival in high IL-6 producers	IL-6 is a proinflammatory cytokine; however, no association with acute rejection has been made.	112
CCR5	Improved long-term graft survival; no association with acute rejection	CCR5 is chemokine receptor important in inflammatory immune responses. CCR5-△32 SNP results in a nonfunctional CCR5.	113
MCP-1	Reduced graft survival; no association with acute rejection	Only homozygous inheritance of this allele had an impact on graft survival.	114
CTLA-4	Acute rejection	Association is stronger in liver transplantation.	84–86,107

CCR5, C-C chemokine receptor type 5; *CTLA-4*, cytotoxic T lymphocyte antigen 4; *IFN-γ*, interferon -γ; *IL*, interleukin; *MCP-1*, monocyte chemotactic protein-1; *SNP*, single nucleotide polymorphism; *TNF-α*, tumor necrosis factor-α.

has been an explosion of reports using this technique to study physiological and pathological gene expression in the experimental and clinical setting. DNA microarray technology involves the RT-PCR, enabling analysis of gene expression for thousands of transcripts in a single step with minimal amount of sample, albeit with slightly diminished sensitivity compared with PCR. Two methods of analyzing gene expression at the whole genome level are cDNA and oligonucleotide microarrays.[88,89] Both of these technologies involve immobilizing nucleotide sequences onto a surface and reading intensities of fluorescent molecules conjugated to mRNA complementary to sequences attached to the array. Microarray technology can be used to generate transcriptomes (microarray-based transcriptional portraits) and identify specific patterns of gene expression that predict and characterize a disease state. Numerous human microarray based studies (summarized in Table 42-3) have been performed in transplantation in an attempt to predict, diagnose, and obtain prognostic information, with respect to acute rejection, response to therapy, delayed graft function, chronic rejection, and tolerance. While significant advances have been made, unfortunately there is little concordance between these studies, and many of the markers identified had no obvious biological relevance to transplantation. This might be attributed to differences in microarray platform used, weak statistical power, and experimental variance particularly relating to sampling variability, with differing amounts of cortex versus medulla represented in the sample, which can greatly affect the pattern of gene expression.

In an attempt to improve the specificity and sensitivity of intragraft gene expression studies for diagnosis of acute rejection, investigators have evaluated the efficacy of using gene expression patterns of a panel of biologically relevant

TABLE 42-3 Gene Microarray Studies in Kidney Transplantation

CLINICOPATHOLOGIC CORRELATION	TISSUE	KEY GENES	PATHWAYS	REFERENCE
Acute rejection	Renal biopsy	*CD8, CD52, granzyme A, CCL5, CXCL9, MHC, STAT1*	Antigen presentation, IFN-γ responses, cytotoxic T lymphocyte	Saint-Mezard et al[115]
Acute rejection	Renal biopsy	*T-bet, Fas ligand, CD152 (CTLA-4)*	T-helper differentiation, co-stimulation, apoptosis	Hoffman et al[116]
Acute rejection	Blood, renal biopsy	*CD14, CD2, chemokines, IFNγ, TNF, TCR*	Immune response and inflammation	Flechner et al[117]
Acute rejection	Renal biopsy	*TCR, CD20, TNFR, granzyme A, perforin*	Immune response (T- and B-cells), apoptosis	Sarwal et al[118]
Interstitial fibrosis (IF)/ tubular atrophy (TA)	Renal biopsy	*MMP-7, THBS-2, SPP-1, FBN-1*	Fibrogenesis	Rodder et al[119]
IF/TA	Renal biopsy	*CCL5, CXCR4, IL-8, IL-10RA, CASP4, CASP5*	Immune response, cell-to-cell interaction, apoptosis	Maluf at al[120]
IF/TA; graft survival	Renal biopsy	*CPA3, TPSB2, TPSAB1*	Mast-cell associated transcripts (MACAT)	Mengel et al[121]
Creatinine at 1 yr	Wedge renal biopsy at the time of transplantation	*NLRP2, IGJ, RGS5*	Immunity and defense, cell communication, apoptosis	Perco et al[122]
Tolerance	Blood	TGFβ-regulated genes, memory T-cell genes	Immune response	Brouard et al[102]

genes, rather than of only one gene or whole genome analysis. This approach was pioneered in renal transplant recipients by the Strom laboratory, which found that the accuracy of the correlation between gene expression and acute rejection histology was enhanced by simultaneous analysis of three CTL markers—Fas ligand, perforin, and granzyme B—in renal biopsy specimens; if any two of these markers were upregulated, the sensitivity and specificity were 100% for detection of acute rejection histology.[90–95] While many of the activated T-cell gene transcripts present in rejecting grafts encode proteins that are critical for mediating damage of the allograft (see Table 42-3), paradoxically, there are some transcripts such as CTLA-4 and forkhead box P3 (FOXP3) encoding molecules that are linked to suppressor-type immune responses.[94,96] Ongoing investigations are examining the relative proportions and significance of these destructive and protective components.

PROTEOMICS IN TRANSPLANTATON

A *proteome* is a set of all expressed proteins in a cell, tissue, or organism, and a systematic analysis of proteins within a defined system for their identity, quantity, and function is called *proteomics*. Clinical proteomics is a rapidly growing field that promises to improve the understanding of the pathophysiological mechanisms underlying rejection and tolerance, and may permit the identification of novel biomarkers and targets for therapeutic intervention. The limited proteomics published to date in transplantation have thus far failed to reveal new avenues of exploration.[97,98]

BIOMARKERS IN TRANSPLANTATION

A biomarker is classically defined as a biological molecule whose presence indicates a disease state or a high likelihood of developing a disease or a specific disease phenotype or outcome. Biomarkers could either have a functional relevance, by virtue of their association with the pathophysiology of the disease or be surrogate biomarkers representing bystanders or downstream consequences of complex pathophysiological disease process. Biomarkers range from RNA transcripts, cellular products, soluble cytokines, and proteins that localize in a cell that can be used to diagnose, stratify treatment, monitor therapeutic response, and predict outcomes. Table 42-4 lists potential biomarkers in kidney transplantation.

Sample Source: Biopsy Tissue versus Blood versus Urine

In biomarker discovery, some consideration needs to be given to what constitutes the most appropriate sample for performing gene or protein expression analysis. Allograft biopsy material (when adequate) clearly represents what is happening in the graft. However, biopsies are expensive and expose the patient to a small risk of complications. Also, the cellular composition of the sample is markedly heterogeneous and includes glomeruli, tubules, interstitium, and vessels in addition to leukocytes. Techniques for laser capture microdissection of areas of interest for further analysis have been developed that may in due course address the heterogeneity of biopsy tissue.

In contrast, blood and urine are readily accessible. Blood interacts with every organ in the body, including the renal allograft, and plays a crucial role in immunity and inflammation. Blood sampling enables collecton of large samples, and is highly amenable to standardization of technical procedures. Peripheral blood leukocytes (PBL) share more than 80% of the transcriptome with many tissues including the kidney.[99] In kidney transplant recipients, CTL gene expression in PBL correlates with rejection.[100] Recent studies using PBL have identified a set of genes that could serve as a molecular signature of tolerance.[101,102] More specific profiling information may be obtained if the cells are sorted before gene expression analysis. The use of blood-proteomics for biomarker discovery, however, is hampered by important technical limitations. On the other hand, analysis of urine is noninvasive and may be particularly relevant and attractive in kidney transplantation, because the lymphocytes present in

TABLE 42-4 Potential Biomarkers in Kidney Transplantation

BIOMARKER	SAMPLE	CHARACTERISTIC	REFERENCE
Perforin and granzyme B	Urine	Diagnosis of acute rejection	103,123
FOXP3	Urine	Diagnosis of acute rejection	123–125
IP-10 and CXCR3	Urine	Prediction of acute rejection and graft function at 6 months	126,127
KIM-1	Urine	Prediction of acute rejection and graft loss	128,129
NGAL	Urine	Prediction of delayed graft function	130,131
RBP	Urine	Prediction of chronic allograft dysfunction	132
β_2-microglobulin	Urine	Prediction of acute rejection	98
α_1-microglobulin	Urine	Prediction of acute rejection and chronic allograft dysfunction	133,134
IL-18	Serum/urine	Prediction of acute rejection and delayed graft function	130,131,135
sCD30	Serum	Prediction of graft loss	136
[C4d]FlowPRA	Serum	Prediction of C4d positive AMR	137
Tibbles-1	Blood	Biomarker for chronic AMR	138

AMR, antibody-mediated rejections; *CXCR3*, chemokine receptor-3; *FOXP3*, forkhead box P3; *IP*, interferon-inducible protein; *IL*, interleukin; *KIM-1*, kidney injury molecule-1; *NGAL*, neutrophil gelatinase-associated lipocalin; *sCD30*, soluble CD30; *RBP*, Retinol binding protein.

the urine have undoubtedly been routed through the kidney. Therefore, the status of such cells might accurately reflect the status of graft-infiltrating lymphocytes. Consequently, in kidney transplant recipients, CTL effector molecule gene expression profiling of urinary sediment correlated with that seen in corresponding renal biopsy specimens and predicted acute rejection with comparably high sensitivity and specificity.[103] Similarly, urine proteomics allows sampling of the entire transplanted kidney and therefore should more accurately reflect the changes in the graft.

Validation Strategies

Because of the relatively high rate of false-discovery associated with microarray-based studies, cross-validation is required for the confirmation of microarray results in terms of differential gene expression and statistical significance.[104] Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) remains the gold standard for validation of microarray discovery. Some have proposed validation by completely independent teams.[104] Others have suggested safeguards such as insisting on evidence that associations are biologically plausible and test results that have a solid biological underpinning should be given more weight.[105] However, it is reasonable to consider novel genes without such prior biological association to facilitate discovery of new genes or pathways associated with disease that may not be expected from the existing literature. Similarly, functional and biological validation of biomarkers discovered using proteomics technologies is warranted.

SUMMARY

Assessment of alloreactivity may permit the understanding of mechanisms of allograft rejection, guide future research and identification of patients at risk of rejection and potential candidates for minimization or tailoring of immunosuppression, and perhaps confirm or even predict a tolerant state for complete withdrawal of immunosuppression. High throughput technologies will probably accelerate this process of discovery. Ongoing research in translational genomics and proteomics will probably reveal further benefits of integrating proteogenomics information, clinical data correlation, bioinformatics, and statistics in the development of molecular-clinical diagnostic assays.

There already is a plethora of assays available to assess the alloimmune response; however, these tests need to be validated by large scale multicenter, international studies and approved by regulatory authorities before they can become part of standard of care for our patients. It is likely that a battery of tests, rather than a single assay, will be required for early, definitive and noninvasive diagnosis of rejection, permitting practitioners to choose among immunosuppressive therapies, measure net immunosuppressive state, monitor allograft function, and predict outcome and tolerance.

A full list of references are available at www.expertconsult.com.

Chapter 43

CHRONIC KIDNEY DISEASE IN NONKIDNEY TRANSPLANT RECIPIENTS: HEMATOPOIETIC CELL AND SOLID ORGAN TRANSPLANTATION

Akinlolu O. Ojo, M.D., Ph.D.

At the end of 2008, more than one million people worldwide had undergone allogeneic transplantation with solid organs (heart, intestine, kidney, pancreas, liver, lung and their combinations) and hematopoietic cell (HCT) or composite tissue transplants. Although kidney transplantation is the commonest form of allogeneic transplantation, accounting for more than 50% of solid organ transplantation in Westernized countries, and nearly all of solid organ transplantations in the developing countries; recipients of nonrenal organ transplant (i.e., heart, lung, liver, pancreas, and their combinations) and HTC outnumber kidney transplant recipients in the aggregate. These large and rapidly growing populations of nonrenal solid organ and HCT recipients suffer an excessively high rate of chronic kidney disease (CKD). Compared to the general population, the incidence rates of National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD stage 5 (end-stage renal disease [ESRD]) is 16 times and 55 times greater in HCT and nonrenal solid organ transplant recipients, respectively.[1,2] The risk of developing ESRD following HCT or nonrenal organ transplantation is 1.7% to 3% annually—a risk rate that is significantly higher than the risk of nondermatological posttransplantation malignancy.[1] Consequent on the improved survival of nonrenal transplant recipients, the risk period ("opportunity") for development of CKD after transplantation has lengthened such that CKD is now the leading long-term complication outside of the transplanted organ for heart, liver, and lung transplant recipients.[3–8] This chapter considers the epidemiology, pathogenesis, and management of CKD in HCT and solid organ transplant recipients excluding type I diabetic recipients of pancreatic allotransplantation. There are no data concerning development of CKD in recipients of composite tissue allografts as yet, and therefore this topic will not be further explored in this chapter.

CHRONIC KIDNEY DISEASE IN HEMATOPOIETIC CELL TRANSPLANTATION

Etiology and Pathogenesis

Both allogeneic and autologous HCT, and stem cell transplantation, are associated with an increased risk of CKD. Approximately 25% of HCT recipients develop CKD at a median of 191 days posttransplantation[9] with a cumulative incidence of CKD ranging from 17% to 66%.[10] Table 43-1 shows the incidence rates of CKD and the definition used in different cohorts of HCT recipients.[10] The major etiological factors for CKD after HCT (Table 43-2) include acute kidney injury, thrombotic microangiopathic injury, chemotherapeutic myeloablative regimens, and calcineurin inhibitor (CI) toxicity.

TABLE 43-1 Incidence of Chronic Kidney Disease after Hematopoietic Cell Transplantation

DEFINITION OF CKD	NUMBER OF PATIENTS	TIME OF ONSET AFTER HCT	INCIDENCE OF CKD	REFERENCE
Doubling of baseline SCr or CrCl <50 ml/min/1.73 m^2 by Schwartz formula	64 children	>60 days	28%	Van Why, 1991[35]
>25% decrease in GFR (Cr-EDTA)	22 children, 50 adults	1.5 to 24 months	47.2%	Lonnerholm, 1991[36]
GFR <85 ml/min/1.73 m^2	66 children	12 months	11%	Kist-van Holthe, 2002[37]
>20 decrease in GFR (inulin clearance)	60 adults	12 to 96 months	56%	Leblond, 1995[38]
GFR <70 ml/min/1.73 m^2	40 children	6 to 60 months	17.5%	Frisk, 2002[39]
SCr >110 µmol/L × 3	84 adults	18 months	20%	Miralbell, 1996[40]
25% decrease in GFR (MDRD equation)	122 adults	6 to 12 months	66%	Weiss, 2006[41]
Elevated SCr on two occasions	286 children, 1307 adults	Days 100 to 517	17.5%	Hingorani, 2006[10]

CKD, chronic kidney disease; *CrCl*, creatinine clearance; *GFR*, glomerular filtration rate; *HCT*, hematopoietic cell transplantation; *MDRD*, Modification of Diet in Kidney Disease Study; *SCr*, serum creatinine.
(Adapted from S. Hingorani, Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment, J. Am. Soc. Nephrol. 17 (7) (2006) 1995-2005.)

TABLE 43-2 Risk Factors for Chronic Kidney Disease after Hematopoietic Cell Transplantation

- Advancing age
- Pretransplantation kidney function
- Calcineurin inhibitor nephrotoxicity
- Tumor lysis syndrome
- Venoocclusive disease
- Conditioning chemoradiation
- Hemolytic uremic syndrome
- Nephrotoxic antibiotics
- Sepsis

Acute Kidney Injury

As in solid organ transplant recipients, acute kidney injury (AKI) after HCT is a common risk factor for posttransplantation CKD. The incidence of AKI after HCT ranges from 30% to 50%. The risk of AKI within 1 month of transplantation is greater for allogeneic HCT (36%) compared to autologous HCT (10%-12%). Forty percent to 50% of patients with AKI after HCT require renal replacement therapy (RRT) either in the form of intermittent hemodialysis or continuous veno-venous hemofiltration and dialysis (CVVHD). A detailed review of AKI after HCT is beyond the scope of this chapter.

It is important to note the following attributes of AKI in HCT recipients considering AKI is a major contributor to subsequent development CKD:

- The risk of AKI increases when the conditioning therapy includes fractionated total body irradiation, although total body irradiation itself may not directly lead to increased risk of CKD.
- AKI presenting within five days of transplantation is usually caused by tumor lysis syndrome or toxicity from the infused marrow.
- The most common period for the development of AKI is between 10 and 20 days after HCT, and the large majority of patients who develop AKI early after HCT present with a clinical disorder that is reminiscent of hepatorenal syndrome (HRS), which is preceded in 90% of patients by venoocclusive disease (VOD) of the liver. VOD is thought to result from hepatic venule endothelial cell injury, induced by radiochemotherapy, leading to thrombosis, fibrin deposition, and sinusoidal and portal hypertension.

Calcineurin Inhibitor Toxicity

CKD occurring more than 1 month after HCT is often the result of CI immunosuppression to prevent graft-versus-host disease (GVHD). The two currently marketed forms of CI (cyclosporine and tacrolimus) are used in combination with prednisone, methotrexate, or mycophenolate mofetil (MMF) to prevent GVHD, which when severe is associated with 50% mortality. CKD in this setting correlates with trough serum cyclosporine levels. In patients without GVHD, CIs are used only for a short time, and chronic CI toxicity is not seen. As more unrelated HCT donor grafts are used, the prevalence of chronic GVHD has increased, and CKD due to chronic CI toxicity appears to increase as well.[1]

Thrombotic Microangiopathy

Chronic kidney disease mediated by thrombotic microangiopathy (TMA) is commonly attributed to radiation nephritis, CI toxicity, acute GVHD, sinusoidal obstruction syndrome, and methylprednisolone therapy.[10] Clinical features of TMA-related CKD in HCT recipients include slowly progressive or subacute declines in renal function (defined as a >50 increase in serum creatinine above baseline or a 50% decrease in creatinine clearance from baseline), microangiopathic hemolytic anemia, elevated L-lactate dehydrogenase (LDH), and negative direct and indirect Coombs test with or without encephalopathy.[11] This form of TMA is observed in 10% to 25% of HCT recipients who present 6 to 12 months after HCT. In mild cases, the hemolytic anemia and thrombocytopenia may be minimal or absent. In the most severe form of acute presentation, the findings include hypertension, proteinuria, hematuria, red blood cell casts, and rapidly progressive renal failure, with microangiopathic hemolytic anemia and central nervous system abnormalities. The prevailing pathophysiological paradigm suggests that TMA in HCT recipients is primarily a consequence of total body irradiation and other types of injuries resulting in endothelial cell damage. Although CI given to prevent GVHD may contribute, TMA has been described in patients

who have not received these agents. The conditioning regimen for HCT usually includes 8 to 14Gy radiation, a dose comparable to that given to patients who develop radiation nephropathy. The histological features and clinical presentation of HCT-associated TMA show a striking similarity to acute radiation nephropathy. The histology of renal tissue (Figure 43-1) reveals enlarged hypocellular glomeruli with mesangiolysis. There is accumulation of spongiform material along the inner aspect of the glomerular basement membrane that extends into the glomerular capillary loops, producing a double contour appearance. There is marked narrowing of the arteriolar lumen caused by mucoid intimal thickening.[10]

Management of Chronic Kidney Disease in Hematopoietic Cell Transplant Recipients

Early diagnosis is critical so that treatment may be instituted before advanced CKD develops. An attempt to should be made to obtain a histological diagnosis by performing a kidney biopsy because of the broad spectrum of underlying causes of CKD in HCT recipients. Quantification of urinary protein excretion is valuable in formulating a presumptive diagnosis but should not be used to determine the need for renal biopsy, because significant glomerular pathology may be present without a significant increase in urinary protein excretion. This misleading scenario of little or no proteinuria is commonly due to the antiproteinuric effect of CI or renal vasoconstriction and vasoocclusive injury due to chronic graft-versus-host disease (c GVHD) or TMA. As in the general CKD population, renin-angiotensin aldosterone system (RAAS) blockade, aggressive control of blood pressure, and modest reduction in dietary protein restriction are important therapeutic options that should be deployed in affected HCT recipients as appropriate. Once TMA is established, treatment is supportive and includes aggressive treatment of hypertension and renal replacement therapy. Angiotensin-converting enzyme (ACE) inhibitors have been shown in animal models of HCT nephropathy to prevent and treat the syndrome and therefore may be preferable to other agents, but definitive proof in humans is lacking. Plasma exchange is not of proven benefit. Although it is unlikely that CI use alone is responsible for causing HCT-associated TMA, attempts at CI dose reduction seem reasonable, but discontinuation is inappropriate given the risks of GVHD. The natural history of patients with HCT-associated TMA is variable. Symptoms may be mild and resolve on their own without specific treatment; others will progress to ESRD. The prognosis of ESRD after HCT is very poor. When there is concomitant GVHD, hemodialysis sessions are often attended by turbulent episodes of hemodynamic instability. Peritoneal dialysis is often ineffective because of poor peritoneal circulation associated with GVHD. One-year mortality rate as high as 75% has been reported in HCT recipients receiving maintenance dialysis. Infection is the leading cause of death. Successful kidney transplantation has been performed using a kidney from the same living donor who provided the hematopoietic cells used for the original transplantation. The result of this same donor kidney transplantation is excellent with the added benefit minimal or no maintenance immunosuppression is necessary for the kidney transplant. Recipients of HCT who undergo deceased donor kidney transplantation require immunosuppression as is typical for kidney transplantation in other settings. HCT recipients who have undergone kidney transplantation should be carefully monitored for immunosuppressant toxicity, because they seem to be more sensitive to the adverse effects of these agents compared to the non-HCT kidney transplant population.

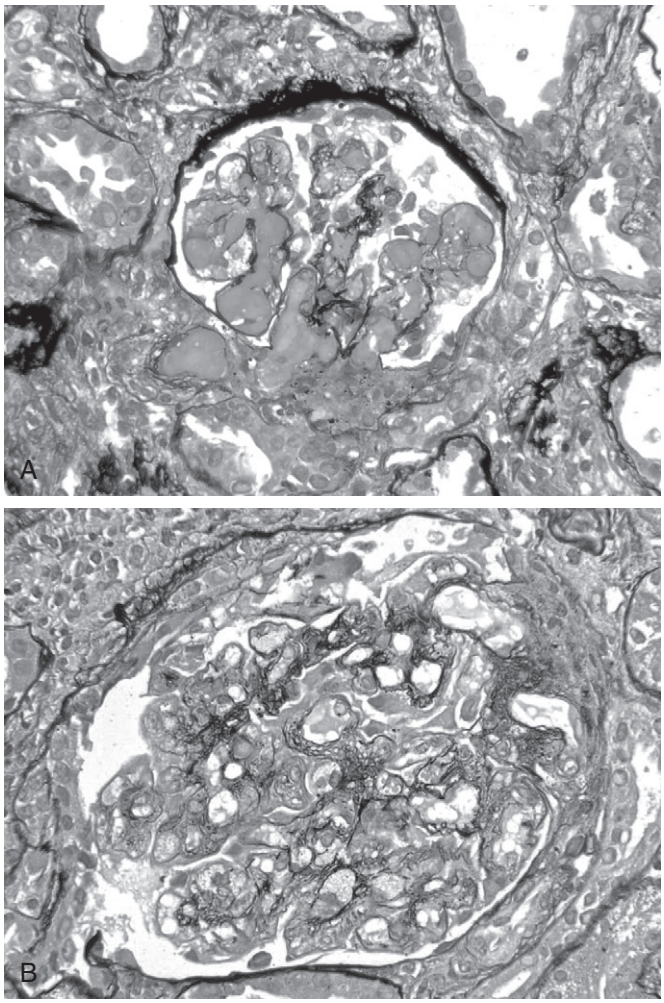


FIGURE 43-1 Changes in the glomerulus in a patient with thrombotic microangiopathy after hematopoietic cell transplantation. Glomerulus shows narrowing of the arteriolar lumen, thickening of the glomerular basement membrane and duplication of the capillary loop, hypocellularity, and mesangiolysis. (From S. Hingorani, Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment, J. Am. Soc. Nephrol. 17 (7) (2006) 1995-2005.)

CHRONIC KIDNEY DISEASE IN HEART, LUNG, LIVER TRANSPLANTATION

Etiology and Pathogenesis

Most studies of CKD in nonrenal solid organ transplantation predate the adoption of the CKD classification developed from the NKF DOQI initiative.[12] The most common definitions of CKD used in many studies prior to the standard proposed in the NKF DOQI initiative[12] are persistent elevation of serum creatinine of greater than 2.0 mg/dl

(176 μmol/L), increase in serum creatinine of 0.5 mg/dl (44 μmol/L) above pretransplantation level for 6 months or greater, and ESRD defined as glomerular filtration rate (GFR) of less than 15 ml/min/1.73 m^2, initiation of maintenance dialysis therapy, or receipt of a kidney transplant. Because of the variable definitions employed, the reported prevalence of CKD in nonrenal organ transplant recipients varies widely from 8% to 10% to more than 70% in some series.[7,13–19] Table 43-3 shows the cumulative incidence rates of CKD stage 4 to 5 of nonrenal transplant recipients in the United States.[2] Even when an unambiguous definition such as ESRD is employed, the prevalence estimates can vary widely. For example, the prevalence of ESRD in liver transplant recipients ranges from 3% to 23%.[6,15,19,20] In both heart and lung transplantation, 8% to 10% of recipients alive at 10 years post-transplantation are on either maintenance dialysis treatment or have received a kidney transplant.[14,21] The prevalence of predialysis CKD has been reported to vary between 25% to 77% in liver transplant recipients.[6,15,18–20] Analysis of data from the Scientific Registry of Transplant recipients in the United States found an ESRD incidence of 1.5% to 2% per year for each type of nonrenal transplant organ among recipients who survived 6 months beyond transplantation (Figure 43-2).[2]

Common Risk Factors

Advancing age, reduced baseline renal function at the time of transplantation, and the occurrence of perioperative AKI have been established as risk factors for posttransplantation CKD in all categories of nonrenal organ recipients.[2,17,22–24] Hemodynamic instability, occurring pretransplantation or intraoperatively, is most commonly due to bleeding, sepsis, or myocardial ischemia and significantly increases the risk of perioperative AKI in heart, lung, and liver transplant recipients. Up to 25% of recipients of these organs require intermittent hemodialysis and or CVVHD in the early postoperative operative.[24,25] These recipients have a two to four fold increased risk of CKD late after transplantation.[17,25–27]

Other risk factors for CKD common to all types of nonrenal organ transplantation include hypertension, diabetes mellitus, and chronic hepatitis C infection.[2,18,20] Hypertension is found in 65% to 90% of heart, lung, and liver recipients. Diabetes mellitus is present in 1% to 2% of patients prior to nonrenal solid organ transplantation, and new onset diabetes mellitus after transplantation develops in 10% to 30%. The presence of pretransplantation chronic hepatitis C virus (HCV) infection confers a 15% greater risk of posttransplantation CKD in all categories of organ recipients.[2] Dyslipidemia is highly prevalent in the organ transplant population, affecting 45% to 80% of liver and thoracic organ recipients, and is a probable but unproven risk factor for CKD. Another major etiological factor is the use of CI (tacrolimus and cyclosporine), which remain the mainstay of posttransplantation immunosuppression (see later discussion).

The relative impact of these common risk factors for CKD has been well-characterized in epidemiological studies. Each 10-year increase in age older than 18 years confers a 36% greater risk of posttransplantation CKD. For reasons that have not been well-elucidated, pediatric recipients are much more susceptible to posttransplantation CKD. Recipients who required RRT within the 6-month period prior to the transplant operation are twice as likely to develop CKD in the posttransplantation period, presumably a consequence of incomplete kidney injury resolution. It is not known whether postponing transplantation to allow for further renal recovery prevents further postoperative kidney dysfunction, but in most cases this is a theoretical consideration because the transplantation procedure is often a life-saving procedure with no opportunity for elective timing. The risk of posttransplantation CKD is increased by 38%, 125%, and 240% for postoperative GFR of 60 to 80, 30 to 39, and less than 30 ml/min/1.73 m^2 respectively, compared to recipients with a preoperative GFR of 90 ml/min/1.73 m^2 or greater. Systemic hypertension and diabetes mellitus increase the risk of CKD by 18% and 42%, respectively.

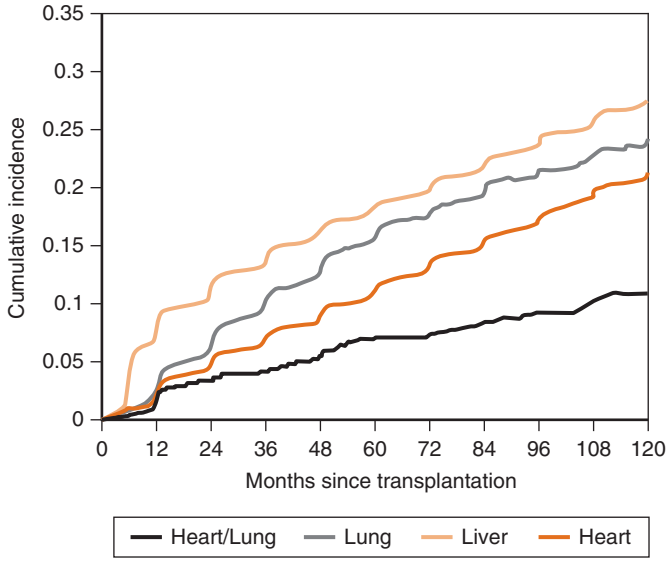
Calcineurin Inhibitor Toxicity

Both of the CI, cyclosporine, and tacrolimus that are in routine clinical use are associated with similar degrees of acute and chronic nephrotoxicity in recipients of nonkidney solid organ transplants.[16] Acute CI nephrotoxicity is principally mediated by reversible intrarenal hemodynamic changes, with higher concentrations of CI also producing tubular injury. Chronic CI nephrotoxicity is characterized by progressive interstitial fibrosis with arterial hyalinosis and intimal hyperplasia (Figure 43-3).

Chronic CI nephrotoxicity is considered to be the dominant etiology in 70% of CKD cases after cardiac, lung, and liver transplantation.[6,28] However, its perceived etiological importance is based on clinical evaluation in the setting of limited histological evidence, because kidney biopsies are rarely performed in solid organ recipients with kidney failure. The reported reasons for the low frequency of kidney biopsy include the finding of atrophic kidneys at the time of referral (a relative contraindication to a safe and informative renal biopsy); the acquired bleeding disorders related to allograft dysfunction in many liver recipients; and the volume overload, heart failure, or pulmonary disease present in many patients which makes it difficult to lie prone or cooperate with respiratory maneuvers required for the biopsy procedure. In one of the few series where renal histology was available, the predominant histological lesions were CI arteriolopathy in 46%, diabetic nephropathy in 34%, and focal segmental glomerulosclerosis (FSGS) in

TABLE 43-3 Cumulative Incidence of Chronic Kidney Disease Stage 4 to 5 (GFR ≤30 ml/min or Less 1.73 m^2) in Nonkidney Organ Transplant Recipients

	TYPE OF ORGAN TRANSPLANTED				
TIME SINCE TRANSPLANTATION	HEART	HEART-LUNG	INTESTINE	LIVER	LUNG
12 months	1.9%	1.7%	9.6%	8%	2.9%
36 months	6.8%	4.2%	14.2%	13.9%	10%
60 months	10.9%	6.9%	21.3%	18.1%	15.8%



	Time since transplantation (months)										
	0	12	24	36	48	60	72	84	96	108	120
Organ	Number of subjects at risk										
Heart/ Lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7643	5633	4316	3184	2327	1629	1136	745	468	258	133

FIGURE 43-2 Cumulative risk of CKD stage 4 to 5 in 69,321 nonkidney solid organ transplant recipients in the United States.

34%.[28] In a series of 44 liver transplant recipients with ESRD who underwent diagnostic kidney biopsy, the predominant etiological diagnosis was CI nephrotoxicity in 73%, FSGS in 7%, cystic kidney disease in 7%, and other diagnoses in 7%.[6] In one study of heart transplant recipients, lesions attributable to CI toxicity were found in 60%, hypertensive nephrosclerosis in 30%, FSGS in 16%, and diabetic nephropathy in 6%. The reason for the high incidence of CI toxicity in nonrenal as opposed to renal transplantation is not fully understood. It may in part be explained by the higher CI serum levels sometimes recommended compared to renal transplantation. It also has been proposed that the denervated state of the renal transplant may afford some protection from CI toxicity compared to the native kidney, although evidence to support this hypothesis is lacking. Progression of renal disease often continues even after withdrawal of CI. Figure 43-3 depicts the course of renal function in calcineurin-treated organ recipients along with the critical impact of other risk factors.

Thrombotic Microangiopathy after Nonkidney Solid Organ Transplantation

As is the case with HCT, TMA after solid organ transplantation is characterized by microangiopathic hemolysis and thrombocytopenia, and renal failure may occur at any time from a few weeks to 10 years after transplantation. It is a major cause of intercurrent AKI episodes after transplantation and has been implicated in posttransplant CKD as well. Cyclosporine- or tacrolimus-induced endothelial injury appears to be the initiating factor in many, but not all, solid organ recipients who develop TMA. Table 43-4 shows the most frequently cited organ-specific risk factors for CKD after liver, heart, or lung transplantation, which are discussed in further detail below in the context of each type of organ transplant. The general implication of these underlying predispositions is that the nephrologist providing posttransplantation care should consider the underlying cause of end organ failure as a risk factor for posttransplantation renal dysfunction, even if clinically overt renal disease was not manifest prior to transplantation.

Impact of Chronic Kidney Disease on Clinical Outcome

CKD complicates the care of organ transplant recipients in a variety of ways. Drug treatment with immunosuppressants, antibiotics, and other agents may be hampered because of contraindications or complex dosing adjustment. The relative imprecision of serum creatinine as an indicator of renal function is not always appreciated, leading to the potential for drug toxicity. Many studies have shown that CKD is

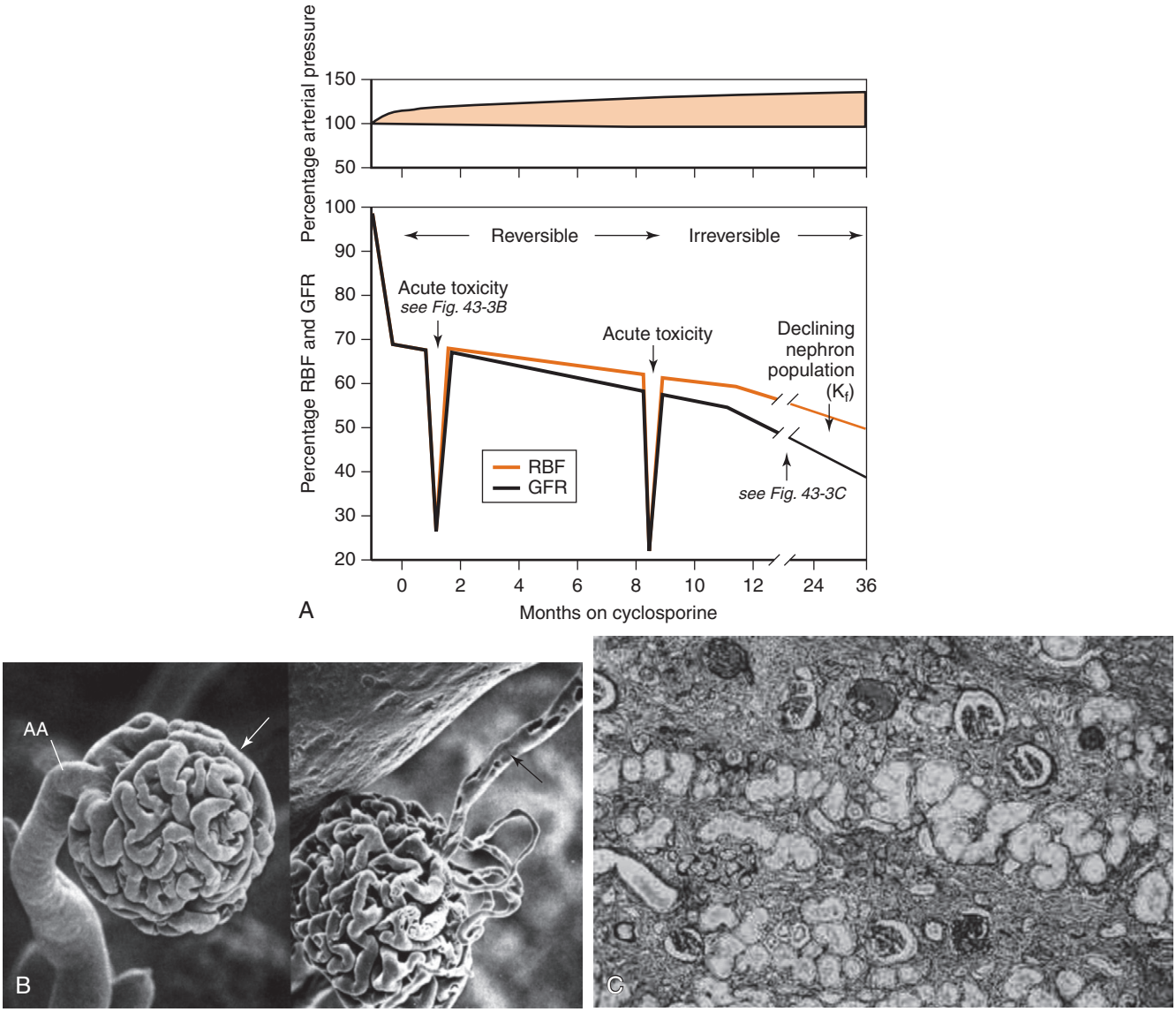


FIGURE 43-3 Pattern of kidney injury under chronic CI therapy. Data from Brian Myers on cardiac allograft recipients at Stanford University demonstrate the course of renal hemodynamics and GFR during chronic cyclosporine (CsA) immunosuppression. Exposure to CsA is accompanied by intense vasoconstriction in the renal capillary bed and elevated systemic vascular resistance manifesting as hypertension *(top graph)*. Hypertension is seen in 80% to 90% of patients treated with CsA for prolonged periods. The *bottom chart* shows renal blood flow (RBF) and GFR over 36 months. Two episodes of acute renal failure were accompanied by near full recovery. However, progressive gradual deterioration of GFR is seen over time along with a steady decline in RBF. After a critical reduction in nephron mass (Kf) from chronic glomerular ischemia, the rate of loss of GFR exceeds the decrement in RBF. At this point, even restoration of RBF to normal is unlikely to mitigate the progressive loss of renal function secondary to maladaptive nephron hyperfiltration in the remnant functioning renal mass. Thus the timing of the elimination of an offending agent that is causing glomerular ischemia (such as CsA and FK506) is of critical importance. Kidney sparing is likely to be realized if the CI is eliminated from the immunosuppressive regimen between 3 and 6 months after transplantation before the nephron loss reaches the stage of inexorability. (Adapted from B.D. Myers, Cyclosporine nephrotoxicity, Kidney Int. 30 (6) (1986) 964-974, and J. English, A. Evan, D.C. Houghton, W.M. Bennett, Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function, Transplantation 44 (1) (1987) 135-141.)

associated with an increased frequency of hospitalization and infectious complications in nonrenal solid organ transplantations. Because of extracellular fluid retention, the severity of preexisting hypertension may worsen. The use of diuretics and the renal disease itself may result in electrolyte abnormalities such as hyponatremia, disordered calcium-phosphate regulation, and acid-base disturbances.

Liver and heart transplant recipients with CKD have a higher incidence of allograft dysfunction, although this relationship may not be causal in nature. The most significant impact of posttransplantation renal disease is an increase in mortality. CKD is associated with a two- to four-fold excess risk of mortality (Figure 43-4). The effect of CKD on mortality is detectable even before recipients reach the advanced stages of CKD.

MANAGEMENT OF CHRONIC KIDNEY DISEASE IN NONRENAL SOLID ORGAN RECIPIENTS

Pretransplantation assessment of kidney function is valuable even when serum creatinine values are within the reference range; malnourished patients with end organ failure may

TABLE 43-4 Organ-Specific Risk Factors for Chronic Kidney Disease Following Heart, Liver, or Lung Transplantation

HEART TRANSPLANTATION
• Systemic atherosclerosis
• Kidney hypoperfusion due to congestive heart failure
• Cyanotic congenital heart disease
LIVER TRANSPLANTATION
• IgA nephropathy
• Hepatitis B- or C-associated glomerulonephritides
• Hepatorenal syndrome
• Oxalosis
• Repeat liver transplantation
LUNG TRANSPLANTATION
• Cystic fibrosis
• Pulmonary hypertension

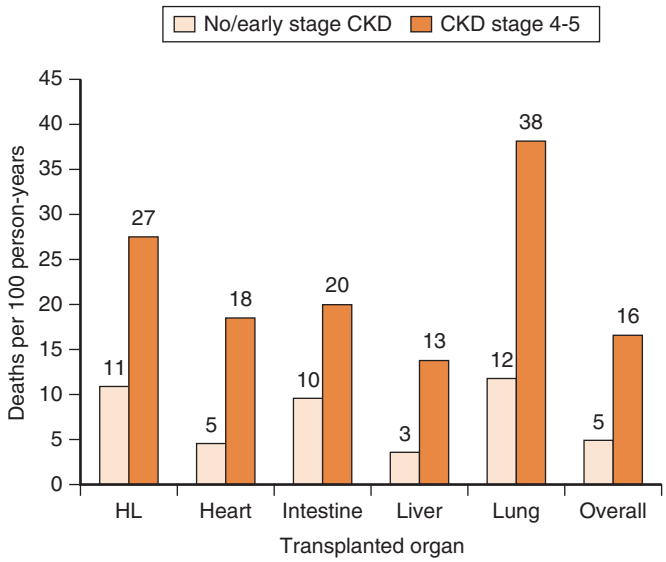


FIGURE 43-4 Mortality rates in nonkidney organ transplant recipients according to the CKD status. Chronic renal failure increases the risk of mortality by 2.5- to 4.3-fold in nonrenal organ recipients compared to transplant recipients without chronic renal disease. *CKD*, chronic kidney disease; *HL*, heart-lung. (Data from OPTN/SRTR 2004 Annual Report. Available at: www.ustransplant.org/annual_Reports/archives/2004/default.htm. Accessed April 20, 2010.)

have unusually low serum creatinine for GFR because of muscle wasting, and a more precise assessment of kidney function, such as isotopic determination of GFR, may be considered and should provide the basis for calculation of medication dosages to minimize drug toxicity. Pretransplantation evaluation should include urinalysis with microscopy of a freshly voided urine specimen. A kidney biopsy should be performed pretransplantation if kidney function is significantly depressed in the absence of a hemodynamic explanation, or if serological evaluation or urinary sediment suggests an active and potentially treatable kidney disease.

Perioperative Care

In the perioperative period, the appropriate type of RRT should be initiated with minimal delay and should be performed without systemic anticoagulation whenever feasible. Close attention must be paid to the composition and volume of all intravenous infusions. In particular, liver transplantation is almost always accompanied by massive intravenous volume expansion; iatrogenic electrolyte abnormalities or coagulopathy may supervene quickly if intravenous fluids are not carefully calibrated.

Calcineurin Inhibitor Avoidance, Withdrawal, or Minimization

The introduction of newer immunosuppressants provides an opportunity to delay the initiation of CI or withdraw CI at various times after transplantation. Induction therapy with basiliximab, daclizumab, or antithymocyte globulin (ATG) is now used in heart, liver, and lung transplant recipients to delay initiation of CI therapy for up 7 to 10 days posttransplantation. This prevents the acute nephrotoxic effect of CI, which would otherwise be superimposed on acute ischemic kidney injury resulting from perioperative hemodynamic instability. Although rational, this approach is yet to be proven in randomized clinical trials to be an effective strategy to minimize postoperative AKI or CKD.

Reduction in dose or complete withdrawal of CI several months to years after organ transplantation has become increasingly common practice in recipients with posttransplantation CKD. These kidney sparing maintenance protocols typically rely on sirolimus or everolimus in combination with MMF to prevent rejection. A number of small studies have shown modest improvement in kidney function following CI withdrawal with sirolimus or MMF substitution in heart and liver transplant recipients with established CKD.[29–31] This improvement may represent relief from the reversible vasoconstrictive effect of CI; studies have shown irreversible histological evidence of chronic glomerular and tubulointerstitial injury as early as 3 to 6 months of continuous CI exposure.[32,33] Reduction in CI dosage or complete elimination can produce sustained improvement in kidney function (Figure 43-5).[30] In one series, a 30% reduction in mean dosage of CI in heart transplant recipients was associated with improvement in mean serum creatinine from 2.8 mg/dl (250 µmol/L) to 1.8 mg/dl (160 µmol/L). However, there are no studies showing reduction in the risk of ESRD with C dosage modification. In some cases, an increased risk of acute rejection has been reported following CI withdrawal. At present, there is insufficient evidence to recommend initial CI-free regimens for heart, lung, and liver allograft recipients.

Calcium channel blockers are potent vasodilators that may counteract the vasoconstrictive effect of CI. Their benefit may be limited to the early stages of CI toxicity when afferent arteriolar vasoconstriction has not resulted in irreversible ischemic injury. The use of calcium channel blockers for this purpose has not been evaluated specifically in nonkidney organ transplantation.

Other treatments shown to ameliorate experimental chronic CI-induced nephrotoxicity include use of antioxidant nutrients, RAAS blockade, nitric oxide enhancement, melatonin, and pentoxifylline. None of these agents has been prospectively evaluated in the clinical setting of nonkidney organ transplantation, apart from pentoxifylline that has not been shown to be beneficial.

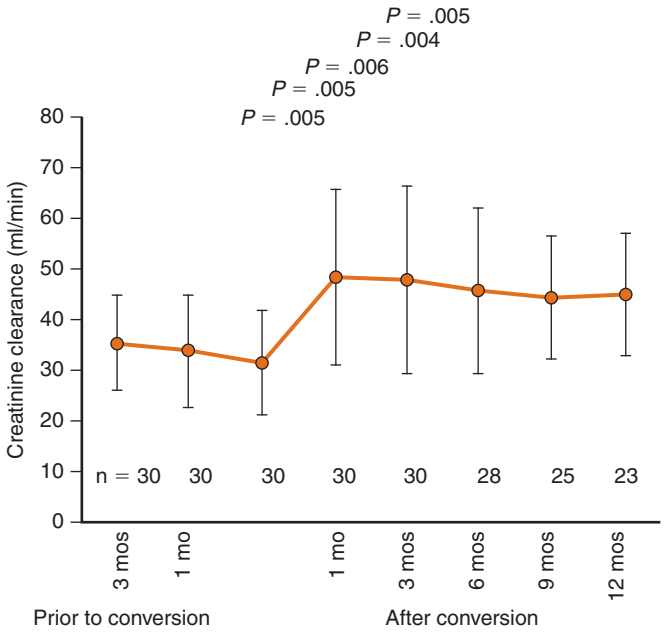


FIGURE 43-5 Creatinine clearance before and after CI withdrawal in heart transplant recipients (n=31). (Modified from J. Groetzner, B. Meiser, P. Landwehr, et al. Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for late cardiac-transplant recipients with chronic renal failure, Transplantation 77 (4) (2004) 568-574.)

Other Treatments

Aggressive blood pressure control with renin-angiotensin blockade using ACE inhibitors and angiotensin receptor blockers (ARB) is key to the treatment of CKD in the nontransplant population and could be expected to have beneficial effects in nonkidney organ transplant recipients, although substantial clinical studies in such patients have not been reported.

Kidney Replacement Therapy

Management of CKD in organ recipients does not differ substantially from that required for a CKD patient without an allograft. The recipient should be assessed for dialysis or kidney transplantation when CKD stage 4 approaches or if the patient enters an accelerated phase of decline during CKD stage 3. Heart, liver, and lung transplant recipients with ESRD who subsequently receive a live or deceased donor have a 44% to 60% reduction in long-term mortality compared to their dialysis-treated counterparts. In one series, the 6-year survival of liver recipients after the onset of ESRD was 27% if they were on maintenance dialysis compared to 71% if kidney transplantation was performed. Preemptive kidney transplantation is also beneficial in these recipients. Nonkidney solid organ transplant recipients with ESRD treated with maintenance dialysis have an annual mortality rate of 28% to 40% compared to 17% to 20% in dialysis-treated ESRD patients who did not receive a prior nonkidney organ transplant. The decision pertaining to whether a potential heart, lung, or liver transplant candidate with advanced kidney disease should undergo multiorgan transplantation that includes a kidney is a difficult one. This decision should be predicated on the duration and severity of kidney function, along with a kidney biopsy to assess chronicity and irreversibility of the underlying kidney disease. Many centers where renal transplantation is performed along with a nonkidney solid organ transplantation use dialysis dependence for 6 or more weeks as a criterion to offer simultaneous kidney transplantation. In other settings, a less stringent criterion (e.g., GFR <30 ml/min/1.73 m^2) could trigger simultaneous kidney transplantation. If a percutaneous kidney biopsy is not feasible, a transjugular approach may be considered. The decision to recommend a heart or liver transplant candidate for simultaneous kidney transplantation should not be based on the severity of kidney dysfunction alone. Despite lack of rigorous evidence of long-term impact on outcome, the number of liver transplant candidates receiving simultaneous liver-kidney transplantation has quadrupled since 2002 and continues to increase at a phenomenally high rate.[34] Such a practice is adversely impacting the number of kidneys available for wait-listed patients with ESRD, because kidneys are preferentially allocated to patients who need a kidney along with a "life-saving" organ transplant. Amazingly, this practice has engendered remarkably little controversy to date.

A full list of references are available at www.expertconsult.com.

Chapter 44

EMERGING STRATEGIES IN KIDNEY TRANSPLANTATION

Marilia Cascalho, M.D., Ph.D., and Jeffrey L. Platt, M.D.

No area of medicine has provoked as much excitement and as many frustrations as transplantation. The excitement stems from the possibility that an organ transplant might quickly restore health. The frustration stems in part from the fact that transplantation can be offered to only a fraction of those with renal failure, owing to the shortage of organs available for transplantation[1] and in part from the need to administer for life toxic immunosuppressive drugs to those who are fortunate enough to receive transplants. Here we discuss new developments in medicine and biotechnology that may add substantially to the excitement and to the frustration.

THE EVOLVING DEMAND FOR RENAL REPLACEMENT

The demand for kidney transplantation already exceeds the supply of organs available for transplantation by a considerable number.[1,2] We speculate here how the demand may change during the ensuing decades.

Advances in medicine will certainly decrease certain indications for kidney transplantation and related therapies. For example, one can imagine that type I diabetes and some types of glomerulonephritis will be prevented or reversed by new immunological therapies. Similarly, the incidence of renal failure caused by hypertension and hyperlipidemia, and hence the demand for transplantation may decrease with better therapies and better delivery of existing therapies. However, we suspect that despite these and other advances, the overall demand for renal transplantation will increase. This increase will follow the increasing use of kidney transplantation and related therapies to preempt disease, from the impact of renal failure as a disease of aging, and from the temptation to preserve productivity of an aging population.

The term *preemptive transplantation* is generally applied to the performance of transplantation earlier in the course of renal failure. As such, preemptive transplantation may provoke a measure of controversy.[3–5] We believe that the application and the controversy may grow substantially. The United States government agency that administers health care programs (Centers for Medicare & Medicaid Services or CMS) currently limits preemptive transplantation to those with glomerular filtration rate (GFR) less than 20 ml/min/1.73 m^2. As tests of blood and urine identify markers of such lethal diseases as cancer of the kidneys and urinary tract, long before the diseases are manifest, clinicians may be tempted to preemptively transplant those with normal GFR who are found to be at risk of developing life-threatening diseases.[6] Preemptive transplantation is sometimes carried out in infants with ambiguous genitalia and the Denys-Drash syndrome, a syndrome characterized by the development of Wilms tumor, congenital nephropathy, and intersex disorders.[7,8] Extending preemptive transplantation to adults with a high risk of tumor formation could add up to as many as 100,000 recipients per year to the list of those awaiting kidney transplants. The scenario is worse for the lung, as demand might increase 100-fold.

Besides changing the demand for organ replacement, preemptive transplantation potentially changes the standard for acceptable replacement. An injured kidney with marginal function might be offered to a patient with kidney failure suffering complications of dialysis, but this kidney might not be acceptable as preemptive replacement in a patient found to be at high-risk for development of renal cancer at some uncertain date in the future. Rather, the preemption

of cancer might provide a compelling indication for application of new technologies for *engineering* kidney replacements that are fully histocompatible with the recipient so that immunosuppression could be avoided.

Changes in the prevalence of diseases associated with renal failure will also heighten the demand for transplantation and related therapies. Type II diabetes and the impact of medical advances in public health on the average age of the population[9–11] will increase demand for transplantation still further, as the increasing prevalence of type II diabetes at each age within the population as a whole certainly broadens the risk of renal failure. This risk may be vitiated if new research into the metabolic syndrome and etiology of diabetes allows the development of specific therapies to counter these problems. However, many will suffer renal failure before those problems can be understood and solved. The number of these subjects will certainly influence demand for renal transplantation into the foreseeable future.

Advances in medicine, while offering hope for treatment and prevention of one or another disease, inevitably increase the number of aging persons in society. Since the function of the kidneys and heart are disproportionately affected by aging, one can expect that the prevalence of renal failure will increase as the average age increases. Advancing age of retirement will likely further increase the demand for transplantation over more conservative therapies for chronic renal disease.

The demand for kidney replacement might also increase with new insight into the impact of renal function on cardiovascular health.[12] Mann and colleagues[13] found that small decreases in glomerular filtration and microalbuminuria correlate with heightened risk of atherosclerosis, ischemic heart disease, and death.[14] If small decreases in renal function are proved to cause rather than simply to mark vascular disease, the indications for and approaches to transplantation might change dramatically. For example, the kidney may clear insulin or phosphate, metabolize vitamin D, or remove a toxin from the blood.[15,16] Such a function might explain why atherosclerosis, ischemic heart disease, and stroke are observed so often in those with small decreases in renal function or microalbuminuria, or both,[15,17,18] and by extension why those who receive a kidney transplant (and thus are uninephric) and those on dialysis suffer an excess of atherosclerotic cardiovascular disease. If the kidney does contribute to cardiovascular health, then the ideal transplants might consist of two kidneys. This concept suggests the possibility that transplantation of the kidneys or of a type of renal cell might someday be undertaken to prevent vascular disease in those with minimal decreases in renal function, and that scenario could clearly increase the demand for renal transplantation by yet another order of magnitude. Changes in the concept of what is renal failure and what level of function is needed for longevity would further heighten demand for transplantation.

Clearly the number of kidneys available for transplantation today is by any measure too small, and even the use of living donors is unlikely to lessen for long what will likely turn to even a more urgent need. Hence, one can anticipate a growing interest in seeking alternatives to the use of human organs for renal replacement. We next will discuss technologies that might be used to augment or replace renal function and some strategies through which those technologies may someday be applied.

EMERGING RENAL REPLACEMENT TECHNOLOGIES

Disparity between demand and supply of organs motivated efforts to apply emerging technologies for replacement or augmentation of renal function. Some of these technologies are discussed below and in recent reviews.[19,20]

Xenotransplantation

For much of the last century, xenotransplantation, that is the use of animals as a source of organs, has been considered the most achievable new technology for replacing the kidney.[21,22] Several obstacles, the most daunting of which is the immune response of the recipient leading to rejection, prevent clinical application today. Detailed consideration of the barriers to xenotransplantation can be found in a collection of recent reviews.[23] Despite these obstacles xenotransplantation of the kidney may still merit consideration, because it would be vastly less expensive and more broadly available than other new technologies.

Clinical xenotransplantation has been tried in the past; the experience is summarized in Table 44-1. Kidneys from nonhuman primates have been used in some trials of xenotransplantation,[21,24,25] and the results in one were quite good.[26]

TABLE 44-1 Early Experience with Clinical Xenotransplantation

YEAR	RECIPIENTS (SURGEON)	SOURCE OF KIDNEY	SURVIVAL	REFERENCE
1906	2 (Jaboulay)	Pig and goat	3 days	121
1909	1 (Unger)	Macaque	< 2 days	122
1914	1 (Ullman)		Unsuccessful	123
1923	1 (Neuhof)	Sheep	9 days	124
1964/1969	13 (Reemtsma)	Chimpanzee (12), macaque (1)	9 months, 12 days	24, 26, 125
1964	3 (Traeger)	Chimpanzee	49 days	126
1964	1 (Hume)	Chimpanzee	1 day	127
1964	6 (Starzl)	Baboon	60 days	128
1964	1 (Hitchcock)	Baboon	5 days	129
1965	2 (Kauffman)	Chimpanzee	4 months	130
1966	1 (Stefanini)	Chimpanzee	31 days	131

We shall focus here on the use of lower animals as a source of kidneys, because among other problems, nonhuman primates such as baboons are too small and not sufficiently numerous to address the need. Larger mammals, particularly the pig, are suitable in size, available in large numbers, and these animals can be genetically engineered and bred.

Barriers to Xenotransplantation Three major factors pose barriers to clinical xenotransplantation. These include the immune response of the recipient against the graft, the physiological limitations of the transplant in the foreign host, and the possibility of transferring infectious agents from the graft to the recipient and potentially to others in society. Because xenotransplantation has been attempted on a number of occasions over the past 100 years, much more is known about these barriers than the barriers to other technologies, such as stem cells and tissue engineering, that have been touted in recent years. Here we emphasize the immune response to xenotransplantation because this response poses the most difficult barrier to application.

The immune responses to xenotransplantation are much more severe than the immune responses to allotransplantation. For a review of this topic, see reference 27. One reason why immune responses to xenografts are severe is that all normal individuals have innate immunity, including xenoreactive natural antibodies, complement, and natural killer cells against xenogeneic cells. Not only can innate immunity destroy a xenograft, it amplifies adaptive immune responses. Another reason why immune responses to xenografts are severe is that xenografts carry a diverse set of foreign antigens against which cellular and humoral immune responses can be elicited (in allotransplants, the main foreign antigens are major histocompatibility complex (MHC) antigens).[28] Immune responses to xenografts might also be severe because immune-regulation, which might partially control responses to allografts, may fail to control responses to xenografts.

The Barrier to Xenotransplantation of Cells and Tissues Although all foreign transplants, xenografts and allografts, elicit immune responses, the impact of these responses depends to the greatest extent on whether the graft consists of isolated cells or tissues on the one hand or a vascularized organ on the other. Examples of cell and tissue transplants include isolated islets of Langerhans used to treat diabetes, isolated hepatocytes used to correct hepatic failure or deliver a therapeutic protein, and xenogeneic fetal kidney, which after implantation becomes vascularized by in-growth of blood vessels of the recipient.[19,29,30]

The Barriers to Transplanting Cells and Tissues The main barrier to transplanting xenogeneic cells and tissues is cellular rejection (Figure 44-1). Cell-mediated immune responses to xenotransplantation are thought to be especially severe[28,31,32] and may, in our view, be further amplified by the humoral immune reactions and by failure of immune regulation between species.[27,33] Some fundamental aspects of the cellular immune response to xenotransplantation have been reviewed by us[27,34] and others.[35,36] What is pertinent to mention here is that, despite the severity of cell-mediated rejection of cell and tissue transplants between disparate species, it appears to be subject to control by immunosuppressive agents currently available.[37] In fact, under some conditions, xenogeneic cellular grafts survive and function without immunosuppression.[37] Thus if one were to identify or engineer a xenogeneic cell or cell line that could replace critical metabolic functions of the kidney, that xenograft might be undertaken today without new methods of immune modulation.

The Barriers to Xenotransplantation of Vascularized Organs Unfortunately, the barriers to transplantation of whole organs, such as the kidney, are much higher than the

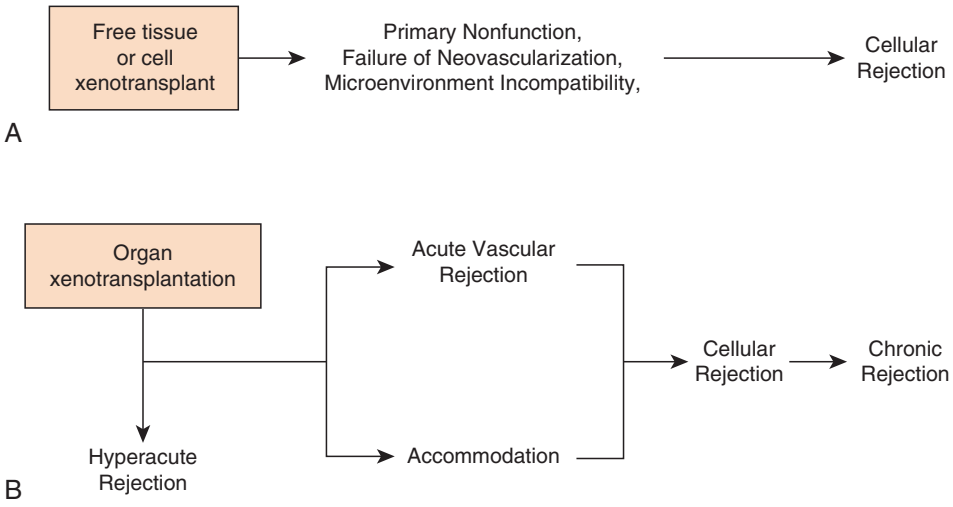


FIGURE 44-1 **Biological hurdles for xenotransplantation. A, The hurdles to transplantation of xenogeneic cells and tissues.** Cell and tissue xenotransplants are subject to failure caused by primary nonfunction that may reflect failure of engraftment or a very rapid immune response. If primary nonfunction is bypassed and the tissue or cells engraft, they are then subject to cellular rejection. Humoral rejection usually is not observed because the blood vessels of recipient origin are not damaged by xenoreactive antibodies and complement and instead serve as a partial barrier to these elements, protecting adjacent grafts from injury. **B, The hurdles to transplantation of xenogeneic organs.** A kidney from one species transplanted into another species (e.g., a kidney from a pig into a human) is susceptible to hyperacute rejection. Hyperacute rejection can be averted by depleting xenoreactive natural antibodies or inhibiting the complement system in the recipient or by engineering the foreign organ to suppress expression of the target antigen (Galα1-3Gal) or to express complement regulatory proteins such as decay accelerating factor. If hyperacute rejection is averted, the xenotransplanted organ is subject to acute vascular rejection. Preventing antibody mediated injury may allow the organ to achieve "accommodation," a condition in which the organ resists injury from antibody and complement and thus does not undergo acute vascular rejection. If hyperacute and acute vascular rejection are prevented, the graft will still be subject to cellular rejection or chronic rejection.

barriers to transplanting isolated cells and free tissues. In whole organ transplants, blood vessels of the transplant are exposed directly to components of the immune system of the recipient, and this interaction gives rise to severe vascular disease in various forms, (see Figure 44-1). The types of vascular disease observed in xenografted organs are the same as those observed in allografted organs; however, the incidence, severity and resistance to therapy are greater in xenografts.

Renal xenografts are quite susceptible to hyperacute rejection, which can destroy the graft within minutes to a few hours.[34,38,39] Hyperacute rejection of porcine organs transplanted into primates is triggered by natural antibodies found in all immunocompetent people and higher primates, specific for galactose-alpha-(1-3)galactose (Galα1-3Gal), a saccharide expressed by pigs and other lower mammals.[40] The binding of these antibodies activates complement, leading to rapid insertion of terminal complement complexes into endothelial cell membranes,[39,41] causing loss of vascular integrity and formation of platelet thrombi that characterize hyperacute rejection.

What makes hyperacute rejection of xenografts especially severe is that activation of complement in the graft is poorly controlled by endogenous complement regulators such as decay accelerating factor, membrane cofactor protein, and CD59.[42] These proteins function poorly across species, and consequently, the complement regulators in a porcine organ would provide only a low level of protection against human complement.[34] Consistent with this concept, organs from transgenic pigs expressing human complement regulatory proteins are protected from hyperacute rejection.[43,44] Today, pigs expressing these proteins or lacking Galα1-3Gal have been widely used in experimental studies, and hyperacute rejection is no longer viewed as a substantial barrier to xenotransplantation.[44,45]

If hyperacute rejection is prevented, renal xenografts become susceptible to a condition we have called acute vascular rejection.[46,47] Acute vascular rejection, sometimes called acute humoral rejection or delayed xenograft rejection, may well be the main hurdle to clinical application of xenotransplantation.[33,48,49] Acute vascular rejection appears to be caused by xenoreactive antibodies that bind to the xenograft, causing *activation* of endothelium in the graft.[50–52] Whereas the endothelium of normal blood vessels promotes blood flow and inhibits thrombosis and inflammation, activated endothelium promotes vasoconstriction, thrombosis, and inflammation, giving rise to the picture of ischemia and thrombosis characteristic of acute vascular rejection of xenografts.[47,53] These pathophysiological changes in endothelium are due, at least in part, to a coordinated elaboration of tissue factor, plasminogen activator inhibitor type 1, E-selectin and thromboxane A2, and other products of genes induced by the action of xenoreactive antibodies, small amounts of complement or platelets.[34,49,51,54] Because acute vascular rejection is thought to be the main biological obstacle to xenotransplantation of organs, much effort is now directed at developing the means to prevent or treat this disorder. Here we summarize the main approaches.

One way to prevent acute vascular rejection may be to suppress the production of xenoreactive antibodies by drug therapy or through induction of tolerance. Various approaches to tolerance have been tried;[54] however, most approaches effective in rodents have not proven applicable in humans. One approach that might be effective in humans is the engraftment of hematopoietic cells of the donor.[55,56] This approach has been combined effectively with transplantation of xenogeneic thymus to yield some promising results in xenografts of kidney and heart engineered, as described later, to lack of expression of Galα1-3Gal.[44,57] Similar results have been achieved by removal or blocking of Galα1-3Gal in recipients of organs expressing human complement regulatory proteins.[56] Unfortunately, these and other combinations of treatments have thus far failed to yield enduring survival of vascularized xenografts.

Another way to prevent acute vascular rejection might be to eliminate the antigens targeted by xenoreactive antibodies. Although porcine cells express many antigens potentially recognized by the human immune system, the main antigen target is Galα1-3Gal.[55] Recent progress in the cloning of pigs[58–60] and in gene targeting[61] makes it possible to knock out the gene encoding the enzyme (α1,3-galactosyltransferase) responsible for synthesis of this saccharide.[62–64] Pigs lacking this enzyme have been produced and studied as a potential source of xenografts. Organs lacking Galα1-3Gal do not undergo hyperacute rejection but do suffer from what appears to be acute vascular rejection,[65] possibly caused by antibodies directed against other antigens.[66–68]

Still another approach to preventing acute vascular rejection may be the induction of *accommodation*.[58,69] First described in organs allografted across ABO-blood group barriers,[70,71] accommodation is an acquired resistance of an organ to immune-mediated injury.[34] Accommodation has been used to prevent acute vascular rejection in rodents and, arguably, in pig-to-primate xenografts.[56,59,62]

How can accommodation be reliably induced and what mechanisms underlie it? Accommodation might reflect a change in xenoreactive antibodies or a change in the antigens in the graft;[60] however, experimental work in xenograft models suggest accommodation results at least in part from an acquired resistance of the graft to humoral injury.[56] Consistent with the latter possibility are experiments showing that endothelial cells exposed to xenoreactive antibodies acquire resistance to complement mediated injury, owing to the increased expression of CD59[72] and other inhibitors of injury.[62] Studies in rodents have shown that accommodation is associated with expression of genes such as *B-cell CLL/lymphoma 2* (*Bcl-2*) and *hemoxygenase-1* (*HO-1*) that confer protection against toxic injury.[63] Organ grafts deficient in HO-1 are subject to severe vascular injury,[64] related perhaps in part to deficiency of carbon monoxides generated by HO-1.[73] However, HO-1 also is expressed by rejecting grafts,[66] and efforts to prevent vascular injury by expression may not be sufficient to induce a state of accommodation, as grafts with increased expression of HO-1 or CD59, or both, may still undergo acute vascular rejection.[74–75]

Besides hyperacute and acute vascular rejection, xenografts are susceptible to cellular rejection, and presumably to chronic rejection.[67] Cellular rejection may be difficult to control for reasons discussed in the section on cell and tissue transplants. To the extent that chronic rejection is caused by an immune response to the graft, as some experimental evidence suggests,[68] then it should be common and severe in xenotransplants. If chronic rejection is caused by qualities of the graft, such as preservation time, ischemia, and donor age, then it should not be much of a problem. In any case,

since xenotransplantation offers an unlimited supply of organs, the impact of chronic rejection may be less serious, as the chronically rejected organ can be replaced.

Physiological Hurdles to Xenotransplantation Studies in which porcine kidneys have been transplanted into nonhuman primates suggest that they function sufficiently in a human to sustain life.[76] Some have postulated that xenografts may be plagued by physiological incompatibility between the coagulation system of the recipient and endothelium or other cells of the xenograft.[57,70,71,77] We are not as yet persuaded about the importance of this barrier. Rather, the main functional impairment of these xenogeneic organ grafts is from rejection, and aberrant coagulation is rarely seen in the absence of immunity. That is not to say the coagulation system is controlled normally in xenograft but that thrombosis and clotting are controlled by compensatory changes. Porcine erythropoietin does appear to work poorly on human cells, so supplementation with the human hormone would probably be needed if xenotransplantation were to be applied. While other defects might still be discovered, these defects are probably no worse than abnormalities imposed by dialysis.

Infectious Agents Another barrier to xenotransplantation is the risk of transferring an infectious agent from the graft to the recipient.[78,79] Infection should be less severe a risk in xenotransplantation than in allotransplantation since the animal source can be raised in an environment free of known pathogens and the organisms associated with the animal can be fully characterized. However, breeding or special handling cannot eliminate endogenous retroviruses of the pig, and that in turn raises the question of whether one or another of these viruses might be infectious for humans.[80]

The porcine endogenous retrovirus (PERV) can infect human cells in culture and in in vivo model systems;[81] hence this virus might be transmitted from a xenograft to a recipient and possibly more widely in the population. However, studies of human subjects who received experimental xenografts or treatment with porcine cells have failed to reveal even a single instance in which PERV has been transmitted to a human subject.[82] Moreover, a recent study suggests that those viruses known at present could be eradicated from pig herds being bred for xenotransplantation.[83] While the question of relevance of PERV to public health cannot be entirely dismissed, the question may now be viewed as one that could be resolved by careful attention to the recipients of xenografts, rather than as a reason for abandoning xenotransplantation.[84]

Toward Clinical Xenotransplantation of the Kidney Although still to be solved, the immune response to xenotransplantation and its impact on the graft may well be addressed in the coming years. Once xenotransplantation becomes immunologically and biologically feasible, interest will be driven by what we think will be the very low cost of using intact organs harvested from pigs compared to the cost of using engineered tissues or devices. The main question then should not be whether xenotransplantation is feasible, but rather whether the physiological cost of immunosuppression and immune modulation needed to allow the prolonged survival and function of a xenograft justify this approach to renal replacement. For the patient with renal failure, this biological cost may well be justified, and xenotransplantation might be welcomed. However, one cannot foresee using xenografts as the ideal replacement for organs removed to preempt disease.

On the other hand, cell and tissue xenografts might achieve widespread use. Because cell and tissue xenografts are not susceptible to injury from antibodies of the recipient[40] and loss from cellular rejection is not life threatening (unlike loss of heart, liver or lung xenograft), these grafts might be tested soon. Further, if the xenotransplantation of a renal cell or another cell suitably engineered could overcome the vascular disease putatively caused by small decrements in renal function or microalbuminuria, such grafts might gain widespread application.

NEW TECHNOLOGIES FOR REPLACING OR AUGMENTING RENAL FUNCTIONS

The possibility that the demand for transplantation might grow substantially, as discussed above, impels consideration of technologies other than organ allotransplantation for the treatment of renal disease. Here we consider technologies that involve transplantation of living cells.

Stem Cells

Stem cells are cells capable of self-renewal by proliferation and of generating at least one, and often more than one, differentiated line of cells.[85–87,99,100] Much attention has been directed at the idea that stem cells might be used to treat disease or restore function to failing organs. The uses include administration of stem cells into injured tissues and the use of stem cells to generate new, mature cells and tissues ex vivo. Here we discuss the potential sources of stem cells and some limitations to application of these cells for augmentation and replacement of renal function.

Stem cells obtained from the inner cell mass of blastocysts are called embryonic stem cells.[74,75,88] Embryonic stem cells are pluripotent, which is to say, they can differentiate into many different types of cells. Because embryonic stem cells can be grown in large numbers and selected in cell cultures, they are commonly used to add or target genes in mice.[89] Embryonic stem cells might in principle be used to repair injured tissues[90,91] or to generate new tissues or organs for transplantation.[92,93]

Three hurdles prevent use of embryonic stem cells for clinical purposes today. First, the use of embryonic stem cells engenders ethical concerns, because isolation of these cells is usually associated with destruction of the early embryos from which they originate. Second, embryonic stem cells and indeed all pluripotent stem cells can and usually do form teratomas and teratocarcinomas after implantation into mature individuals.[74,75] This problem may not preclude use of the cells to generate mature tissues if residual stem cells can be depleted.[94] Third, embryonic stem cells and tissues generated from them would be immunogenic,[78] at least to some extent in any person treated with them, and hence immunosuppression might be needed. These problems raise interest in technologies that might be used to generate pluripotent stem cells from the cells of mature individuals (i.e., the person needing treatment).

Pluripotential stem cells, like embryonic stem cells, can be generated by transferring nuclei from mature cells to immature cell bodies, that is, by cloning.[79] Cloning is accomplished by harvesting nuclei from the cells of one individual and implanting the nuclei in primitive cells such as oocytes or zygotes that have the capacity to reprogram the nuclei. *Reprogramming* involves removal of covalent modifications of DNA, restoration of the ends of chromosomes, and expression of appropriate transcription elements that allow the new cell to function as totipotent stem cells. Cloning by nuclear transfer can generate an entire individual, a process called reproductive cloning, or a tissue or organ, a process called therapeutic cloning. One advantage of therapeutic cloning is that it generates cells with the same histocompatibility antigens as the individual from whom the nucleus is obtained (except for mitochondrial antigens, which derive from the oocyte). Another advantage is that the cloned cells, like embryonic stem cells, can develop into any tissue. However, how to make stem cells form an organ ex vivo is still unknown.

Using human embryonic cells for cloning mature cells would face the same ethical barriers as using human embryonic stem cells, since the immature cells might be obtained by destroying human embryos; however, cloning has been accomplished using embryonic cells from different species.[95–97] Xenogeneic cloning might not pose ethical problems but it might engender immunological reactions. Stem cells generated by nuclear transfer derive their mitochondria from the primitive embryonic cells used to reprogram the cloned cell, and the DNA foreign mitochondria encode minor histocompatibility antigens. Hence immunosuppression might be needed or the graft might fail over a period of time.

The most promising approach to generating pluripotent stem cells involves reprogramming of the cells by expressing primitive genes. Cells in which reprogramming is induced are called induced pluripotent stem (IPS) cells.[98,99] IPS cells are generated today by introducing several genes, the expression of which provokes reprogramming. Generating pluripotent stem cells in this way would overcome most ethical hurdles and would assure that the pluripotent cells, and their progeny would be fully histocompatible with the individual from which the reprogrammed cells were obtained. However, reprogramming cells by transfection would raise concerns about the potential development of tumors. This concern might be addressed in part if *reprogramming factors* could be delivered as proteins rather than as genes encoding them.[20] Such factors have been partly isolated and tested.[100]

Stem cells can be isolated from adults, and these cells do have the capacity to differentiate into complex structures.[86] The advantages of using *adult* stem cells are that the cells might be isolated from the patient themselves, thus avoiding immune reactions and ethical problems associated with use of totipotent embryonic cells. Adult stem cells can migrate through the blood and take up residence in injured tissues.[87,90] Thus stem cells regenerate diseased tissues. However, effective application of stem cells for regeneration may require overcoming barriers still unknown that prevent the natural stem cells of the patient from regenerating the diseased kidney in the first place. The generating of a whole organ such as the kidney by adult stem cells is less feasible than doing so with embryonic stem cells, because adult stem cells appear to have less ability to proliferate and differentiate. However, adult stem cells might someday be used to provide metabolic functions, as discussed earlier.

Stem Cells and Regeneration of the Kidney Given the attention devoted to the promise of stem cells, one might imagine that pluripotent stem cells and perhaps mature stem cells will someday be used to regenerate diseased or injured kidneys.[101,102] How exactly to coax stem cells to restore the structure and function of a kidney is uncertain. As discussed later, isolated fetal cells and organ rudiments do have the capacity to form an entire organ, a process known as organogenesis, but making less differentiated, less committed cells behave in this way would appear to be a challenge. One application of pluripotent stem cells that might be considered is that of providing whatever metabolic functions are lacking in those with mild renal insufficiency. Given progress in devising methods for coaxing stem cells to serve biosynthetic and endocrine functions,[92] it is reasonable to think that the means could be devised to make the cells secrete erythropoietin or carry out needed metabolic functions. Indeed, one recent report claims to have generated kidney like devices using cloned cells of cattle.[103] However, the method described used cells actually harvested from a fetus, and thus reproductive rather than therapeutic cloning was performed and tissue rather than de novo generated stem cells were used.

Tissue Engineering

While embryonic stem cells or cloned cells have the capacity to differentiate into any type of cell and contribute to formation of mature tissues and organs, they may not be able to form intact organs, as discussed earlier. Organogenesis, as such, requires cues from complex cell-cell and cell-matrix interactions that may not be easily recapitulated outside the embryo. One way to deliver some of these cues is through tissue engineering, the use of scaffolds consisting of synthetic or biological polymers, to coax growth and development.[104] Tissue engineering has been used to generate heart valves,[105,106] cardiac muscle,[107,108] bone,[109] liver,[110–126] blood vessels,[126,127] nerve[111] and islets.[112] The most successful applications have been engineered cartilage[111–112] and skin.[113] Tissue engineering is not generally thought to be applicable for organ replacement because the matrices in current use do not permit the growth of cells into a sufficient mass or anatomical complexity to yield a whole organ.

Organogenesis

Organogenesis (de novo organ formation) might be used to generate organs for transplantation. Organogenesis has been carried out for experimental purposes for many years. Nephrogenic mesenchyme cultured under suitable conditions has been shown to develop into kidney like structures in vitro.[114] Since human fetal nephrogenic mesenchyme will not be available, what is needed is a way either to use xenogeneic nephrogenic mesenchyme or to drive stem cells to become nephrogenic mesenchyme. Both will be discussed.

Fetal kidney tissues from various sources have been found to mature after implantation into adult animals.[115–117] Organs grown in this way are vascularized by ingrowth of blood vessels of the recipient. Recently Rogers showed that fetal porcine kidney tissue can mature in an adult rat and that the tissue exhibits some renal function.[118] Aside from the question of whether full function could be achieved by this approach, there is the concern that the xenogeneic organs would be destroyed by the immune response of the treated individual,[119] as described above. While immune-injury is an important concern, the immune response is not as severe a hurdle as it might seem. Since the blood vessels in the organ would derive from the animal host,[115] that is, the treated individual, the graft would not be subject to the various types of vascular rejection described earlier, but rather in principle, it would be subject only to cellular rejection. Still preventing cellular rejection would require treatment with immunosuppressive agents,[119] and hence this application would be less appealing for preemptive therapy.

An alternative approach to organogenesis would be to use stem cells originating from the affected individual, perhaps derived by nuclear transfer. As already indicated, these stem cells may lack the ability to grow into an intact organ, but in a natural environment the cells might form nephrogenic mesenchyme.[103] Toward this end, we have proposed that pluripotent stem cells generated using cells of the person to be treated might be implanted into a fetal animal and they acquire the capacity to form a kidney.[120] The human nephrogenic cells might then be harvested and placed into the subject from which the stem cells derived, and organogenesis could proceed further. Under these conditions, the kidney that formed would be fully histocompatible with the treated subject (if pluripotent cells were generated by nuclear transfer, the cells might express foreign mitochondrial antigens). Importantly the newly formed kidney would be fed by blood vessels of the patient,[115] and hence severe immune reactions listed in Figure 44-1 should be avoided. An important limitation to this approach and indeed to application of tissue engineering in general is that it might be too expensive or complex to allow routine application.

APPROACHES TO AUGMENTATION AND REPLACEMENT OF RENAL FUNCTION: A SYNTHESIS

Any discussion of future therapies, particularly complex therapies that might be applied for the augmentation or replacement of renal function, is fraught with hazard. New treatments may eradicate diabetes, hypertension, and glomerulosclerosis, the most common problems leading to renal failure and hence the need to replace renal function. Unforeseen barriers will block some technologies enthusiastically pursued today; other technologies still to be found will eclipse those discussed here. Still, certain predictions can be acted upon without hazard. One can be sure that the demand for augmentation or replacement of renal function will increase owing to the aging of the population, advances in molecular diagnosis, and the extension of medical care to those presently underserved. One can guess with reasonable confidence that availability of allotransplantation will not expand to the same extent. Hence we think a consideration of technologies for the near future is reasonable and prudent. This consideration helps to determine which technologies need to be improved and which new technologies may be needed.

Given the various technologies that might be applied to replacement or augmentation of renal function, what strategies can be envisioned for application in the future? To address that question, we would envision a potential need to match each strategy to a proposed application.

Those with severe chronic kidney disease (CKD) requiring immediate replacement of function might receive renal allografts as a permanent therapy. Such individuals might be candidates for an *engineered* organ, as discussed later; however, in this case, temporary renal replacement would be needed, and an allograft or even a xenograft might serve that purpose. Xenografts have the advantage of unlimited availability and low cost but at present cannot be undertaken because of the immunological barrier. Someday, xenografts might be used as a temporizing treatment until a histocompatible organ replacement can be produced.

For preemptive treatment (e.g., the patient with early diagnosis of renal cancer), the ideal replacement for the kidneys might be organs engineered to be genetically identical to the patient. This approach would avoid use of immunosuppression. One sequence of steps that might generate such an organ is shown in Figure 44-2. The steps include generation of pluripotent stem cells from the person needing treatment. The stem cells might be used to fashion a device;[103] however, we believe the better solution might be to generate nephrogenic mesenchyme, perhaps in a xenogeneic host as described above, and then use it for organogenesis in the patient.[96,120] Applying the approach of the "engineered kidney" is labor intensive and undoubtedly quite expensive, but it would finally address the hurdle of immune compatibility between the graft and the host.

Some renal diseases might be treated by transplantation of cells that provide a hormone or other substance deficient in those with chronic kidney disease. The cells might be derived from pluripotent stem cells and engineered to secrete large amounts of the needed substance or to digest some critical waste substances.

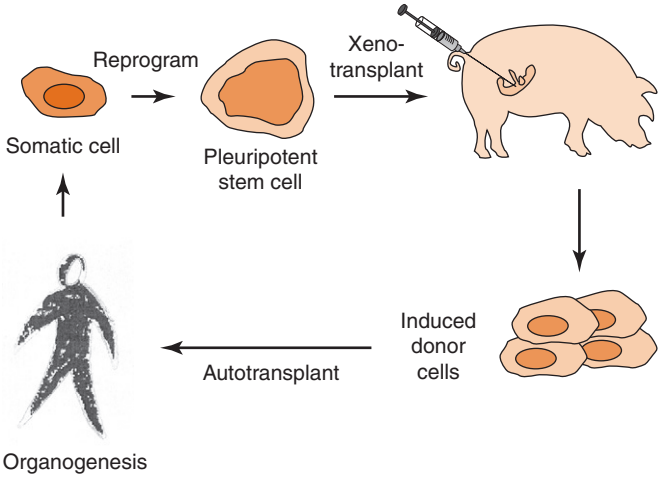


FIGURE 44-2 A potential approach to replacement of the kidney using the multiple technologies of cloning, stem cells, and organogenesis.

Another potential solution for full renal replacement would involve the use of a fully implantable device, which might be envisioned in the coming years, together with a cellular implant that would provide the metabolic functions deficient in the device. The cells used to replace renal metabolic functions would ideally be generated by therapeutic cloning to make them compatible or nearly so with the patient.

ACKNOWLEDGMENT

Work in the authors' laboratories is supported by grants from the National Institutes of Health (HL79067, HL52297) and by a grant from the Bill and Melinda Gates Foundation.

A full list of references are available at www.expertconsult.com.

Chapter 45

CHRONIC KIDNEY DISEASE AND THE KIDNEY TRANSPLANT RECIPIENT

John S. Gill, M.D., F.R.C.P.C., M.S., and
Olwyn Johnston, M.B., M.R.C.P.I., M.D., M.H.Sc.

IS CHRONIC KIDNEY DISEASE AN IMPORTANT ISSUE IN KIDNEY TRANSPLANT RECIPIENTS?

Kidney Transplant Recipients have Decreased Kidney Function

The fact that kidney transplantation incompletely restores kidney function in most transplant recipients has been shown in a number of recent studies. Figure 45-1 shows the prevalence of chronic kidney disease (CKD) in 69,394 adults, first kidney transplant recipients between 1987 and 1997 with graft survival of at least 1 year in the United Stated Renal Data System (USRDS),[1] Glomerular filtration rate (GFR) was estimated at 1, 3, and 5 years after the time of transplantation with an equation derived from the Modification of Diet in Renal Disease (MDRD) Study,[2] and patients were classified by National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD stage.[3] At each time point, the mean GFR was approximately 50 ml/min/1.73 m^2 and the prevalence of K/DOQI CKD stage 3, 4 or 5 was greater than 70%.

Although improvements in immunosuppression have led to an increase in the level of kidney function that recipients of deceased donor transplants establish after transplantation,[4] factors such as the aging of the donor population, the increased use of expanded criteria donors, and donation after cardiac death donors will limit future improvements in kidney function among deceased donor (DD) recipients. Similarly increased use of advanced age living donors (LD) and possibly of LD with isolated medical abnormalities (i.e., hypertension) or with lower predonation levels of kidney function may also limit material improvements in the kidney function established among LD transplant recipients.

Chronic Kidney Disease-Related Complications are Highly Prevalent in Transplant Recipients

Kidney transplant recipients have a high prevalence of CKD-related complications such as anemia, hypertension, hyperphosphatemia, hypoalbuminemia, and acidosis. As in patients with native kidney disease, the prevalence of CKD-related complications increases with declining GFR in transplant recipients. Figure 45-2 shows the mean number of CKD complications per patient in a stable kidney transplantation population at a single Canadian center.[5] Similar findings have been published based on data from the UK Renal Registry.[6]

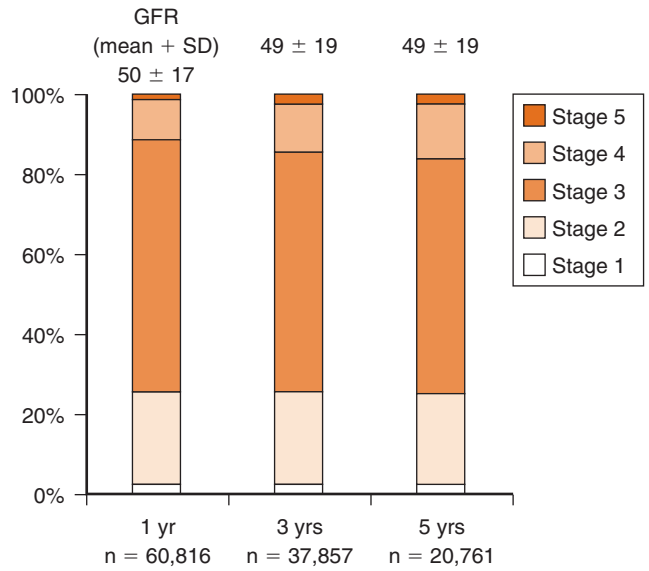


FIGURE 45-1 Mean ± standard deviation (S.D.) of estimated glomerular filtration rate (GFR) (ml/min/1.73 m^2) and prevalence of K/DOQI chronic kidney disease stages among adult first transplant recipients in the United States between 1987 and 1997 at 1, 3, and 5 years after transplantation.

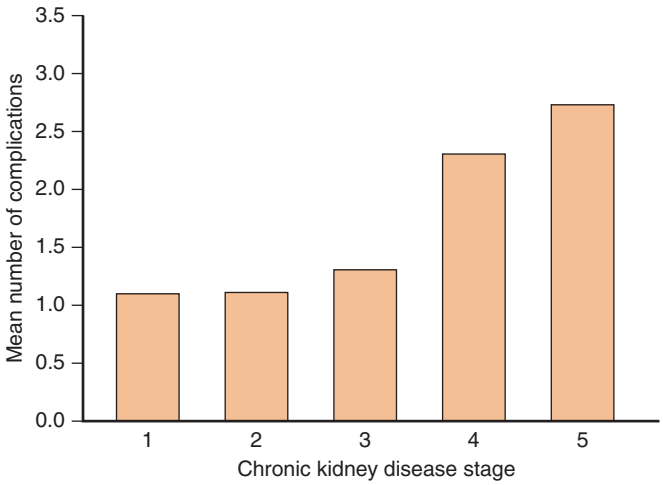


FIGURE 45-2 The mean number of CKD complications per patient by CKD stage. The complications included hypertension (blood pressure ≥140/90 mmHg), serum calcium of less than 8.5 mg/dl, serum phosphorus greater than 4.5 mg/dl, hemoglobin less than 11g/dl, serum albumin less than 3.5 g/dl, LDL greater than 100 mg/dl, and total CO_2 less than 22 mEq/L. (Adapted from V. Karthikeyan, J. Karpinski, R.C. Nair, G. Knoll, The burden of chronic kidney disease in renal transplant recipients, Am. J. Transplant. 4[2] [2004] 262–269.)

There has been Little Improvement in Long-Term Transplant Survival

Despite improvements in immunosuppression, reduction in acute rejection, and improvement in short-term allograft survival, there has been little improvement in long-term transplant survival.[7] Registry data continue to demonstrate a patient survival advantage for those who receive LD compared to DD transplants. Recent data have suggested the importance of premature patient death as an important factor limiting the achievement of long-term transplant survival.[8] Specifically there have been modest improvements in death censored graft survival over time, but virtually no improvement in patient survival after transplantation.[9] These observations suggest that increased emphasis on strategies to improve the survival of transplant recipients, including attention to CKD-related complications, may be the key to improving long-term transplant outcomes.

The Survival of Transplant Failure Patients Remains Poor

A number of recent studies have demonstrated that patients with transplant failure are at increased risk of death.[10–12] The transplant community has only recently appreciated the importance of considering survival after allograft failure as an important transplant outcome.[12] Increased recognition of CKD and CKD-related complications in patients with failing allografts may be an important strategy to improve the survival of failed transplant recipients.

Inclusion of Kidney Transplant Recipients in the Classification of Chronic Kidney Disease

The original K/DOQI Clinical Practice Guidelines for CKD defined CKD as either kidney damage or GFR of less than 60 ml/min/1.73 m^2 for 3 months, irrespective of cause.[3] Kidney damage was defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either pathological abnormalities or markers of kidney damage (i.e., abnormalities on blood or urine tests or abnormal imaging tests). The guidelines also proposed a new severity-based classification of CKD based on the level of GFR. Five stages of CKD were defined and each stage had an associated action plan. The initial K/DOQI CKD guidelines recommend referral to a specialist if the clinical action plan cannot be prepared or if the prescribed evaluation or recommended treatment cannot be carried out.[3] The guidelines further recommend that, in general, patients with GFR of less than 30 ml/min/1.73 m^2 be referred to a nephrologist.

In the initial K/DOQI CKD classification, kidney transplant recipients (KTRs) were included but not emphasized.[3] The inclusion of KTRs was subsequently emphasized in a position statement from Kidney Disease: Improving Global Outcomes (KDIGO) initiative.[13] This KDIGO position statement recommended that all KTRs be considered to have CKD, irrespective of GFR or presence or absence of markers of kidney damage, and highlighted the inclusion of KTRs with the designation "T" to indicate transplantation.

More recently, a KDIGO consensus conference on the care of KTRs[14] recommended that the clinical action plan in the initial K/DOQI CKD classification be amended for KTRs. Table 45-1 summarizes both the initial K/DOQI classification and the recently proposed changes to the clinical action plan. First, estimation of progression of CKD (originally recommended in those with CKD stage 2) and evaluation and treatment of CKD related

TABLE 45-1 Stages of Chronic Kidney Disease and Action Plan for Nontransplant CKD (−T) and Transplant CKD (+T)

CKD STAGE	DEFINITION	CLINICAL ACTION PLAN*	
		NON-TX CKD (-T)	TX CKD (+T)
1	Kidney damage or post-Tx with normal or ↑ GFR (≥90 ml/min/1.73 m²)	Diagnosis and treatment Treatment of comorbid conditions Slowing progression CVD risk reduction	Diagnosis and treatment, treatment of comorbid conditions Slowing progression CVD risk reduction Estimating progression Evaluating and treating complications due to CKD prior to and after Tx Managing Tx specific issues
2	Kidney damage or post-Tx with mild ↓ GFR (60–89 ml/min/1.73 m²)	Estimating progression	
3	Moderate ↓ GFR (30–59 ml/min/1.73 m²)	Evaluating and treating complications	
4	Severe ↓ GFR (15–29 ml/min/1.73 m²)	Preparation for kidney replacement therapy	If evidence of CKD progression, preparation for kidney replacement therapy (patient and family education, dialysis access, preemptive Tx)
5	Kidney failure (<15 ml/min/1.73 m²)	Replacement (if uremia present)	Replacement (if uremia present)

*Include actions from preceding stages.
CKD, chronic kidney disease; *CVD*, cardiovascular disease; *GFR*, glomerular filtration rate; *Tx*, transplant.

complications (originally recommended in those with CKD stage 3) should be applied in all KTRs (CKD stage 1-5). The rationale for this modification is that KTRs carry the burden of preexisting CKD (i.e., hyperparathyroidism, anemia, cardiovascular disease), and consequently, these complications should be addressed even if the GFR is relatively normal. Second, preparation for kidney replacement therapy (originally recommended in those with CKD stage 4) should apply only to KTRs with stage 4 CKD *with* evidence of progressive GFR decline. The rationale for this modification is the recognition that the rate of CKD progression in KTRs may differ from that in other forms of nontransplantation CKD and that KTRs can maintain a stable but low GFR for many years.[8,15]

Possible Advantages of Classifying Transplant Recipients as Chronic Kidney Disease Patients

There are a number of potential advantages of including KTRs in the CKD classification.[16] Increased recognition of CKD may facilitate implementation of therapeutic strategies to delay progression of kidney function decline or prevent CKD-related metabolic complications. Inclusion of KTRs in a simple severity-based kidney disease classification schema may improve communication between clinicians, enhance public education, and facilitate research. Finally, a uniform disease classification and action plan including all patients, irrespective of the need or type of renal replacement therapy (i.e., dialysis or transplantation), may enhance the continuity of patient care.

Transplant recipients have multiple care providers before, during, and after transplantation. Recent publications have shown that transplant recipients are at increased risk of death during transitions between different forms of renal replacement therapy[17] (i.e., during the transition from dialysis to transplantation and the transition back to dialysis after transplant failure), suggesting maintenance of continuity of care in these patients is a significant concern. The overall management of CKD care should be directed by the physician most familiar with CKD. Because aggressive CKD care should begin prior to transplantation and continue after allograft failure, it may be appropriate for a nontransplant physician to direct the CKD care of transplant recipients. Irrespective of who assumes the responsibility for CKD care, communication between the multiple responsible care providers is essential to ensure continuity of care. The following sections outline some of the key considerations of CKD care in transplant recipients before transplantation, during the peritransplant period, during the period of long-term kidney function, and after transplant failure.

CHRONIC KIDNEY DISEASE MANAGEMENT

Chronic Kidney Disease Care Prior to Transplantation

The clinical manifestations of CKD in a given transplant recipient will depend on the duration and burden of CKD prior to transplantation and the level of kidney function achieved after transplantation. Exposure to immunosuppressive medications after transplantation may exacerbate CKD-related complications such as hypertension, diabetes, dyslipidemia, and anemia. Early recognition and treatment of CKD-related complications, maximization of allograft function, and minimization of immunosuppressive-related side effects should decrease the impact of CKD in transplant recipients.

Aggressive CKD care should begin prior to transplantation because the preexisting burden of CKD present at the time of transplantation will not be undone by the provision of a functional allograft. In contrast, many of the complications of CKD such as hypertension, dyslipidemia, anemia, and malnutrition can be prevented or delayed by early detection and treatment prior to transplantation.[18] Prolonged exposure to dialysis before transplantation has been associated with reduced allograft survival,[19,20] and preemptive transplant recipients have an allograft survival advantage.[21,22] The reasons underlying these associations are

somewhat uncertain; however, a lower burden of CKD in patients with no or limited dialysis exposure is a plausible explanation.[23] Reducing dialysis exposure through LD transplantation and preemptive transplantation should be encouraged.

For patients without the possibility of an LD transplant, aggressive CKD management prior to transplantation will become increasingly important because of longer transplant waiting times. The United Network of Organ Sharing (UNOS) waiting list for deceased kidney transplantation is increasing at a rate of 20% per year and was predicted to include an estimated 95,000 patients by 2010.[24] Under present conditions, waiting times of a decade or more are anticipated,[25] and CKD management of waitlisted individuals will be more difficult. Proposed changes to the UNOS kidney allocation schema would prioritize patients with the greatest anticipated increase in survival with transplantation compared to survival with dialysis for transplantation.[26] The implications of the proposed changes on waitlist management have received little attention. However, it is possible that older, more medically complex patients would have increased waiting times for transplantation if the proposed changes are implemented. Additionally, the proposed changes would not increase the predictability of the timing of transplantation. Increased predictability of the timing of deceased donor transplantation has been touted as a potential strategy to improve waitlist management by facilitating investigations and interventions that may reduce perioperative morbidity and mortality.[25,27,28]

Chronic Kidney Disease Care in the Peritransplantation Period

Transplant recipients are at increased risk of mortality in the peritransplantation period compared to waitlisted patients who remain on dialysis. Data from the USRDS and Medicare claims were used to describe the incidence of cardiovascular morbidity and mortality in the peritransplantation period.[28] There was a marked increase in the rate of all cardiovascular events (death, myocardial infarction, congestive heart failure, coronary revascularization, and stroke) during the peritransplantation period. The estimated probability of myocardial infarction, cardiac arrest, and congestive heart failure in DD transplant recipients in the first posttransplantation month was 1.2%, 1.1%, and 5.2%, respectively. About 5% of first kidney transplant recipients will die within the first posttransplantation year.[28] The majority of deaths are due to cardiac causes and patients with comorbid disease (diabetes, peripheral vascular disease, angina), and patients with a longer duration of CKD are at increased risk for mortality. These deaths should be regarded as failures of CKD management rather than failures of transplantation because they result from the accumulated burden of CKD prior to transplantation that may have been prevented by the provision of aggressive pretransplantation CKD care. Posttransplantation factors including the incidence of acute rejection and delayed graft function may contribute to the development of acute coronary syndromes in the peritransplantation period. Delayed graft function may be associated with increase cardiac work due to volume expansion. Because delayed graft function is often predictable, it may be preferable to avoid the allocation of organs at high risk for delayed graft function (i.e., kidneys obtained from donation after cardiac death donors and expanded criteria donors [ECD]) to patients with a high burden of cardiovascular disease. Unfortunately, it is not clear that the implementation of a separate waiting list for ECD kidneys in the United States has decreased peritransplantation morbidity and mortality.[29] In theory, patients waitlisted for ECD kidneys are predicted to undergo transplantation in a relatively short period of time, which should facilitate implementation of investigations and interventions proven to reduce perioperative risks in the nontransplant setting.[30]

Chronic Kidney Disease Care in Patients with a Functioning Allograft

Cardiovascular disease is one of the most important threats to long-term patient survival after transplantation. The management of cardiovascular disease in transplant recipients will continue to be an important component of posttransplantation CKD care because of the increasing age and burden of CKD in these patients. Comprehensive reviews of posttransplantation cardiovascular disease and treatment guidelines for cardiovascular risk reduction are available, and therefore a detailed discussion of these issues is not provided here.[31–33] There is increasing interest in the effect of different immunosuppressive agents on the development and progression of cardiovascular disease. For example new onset diabetes mellitus after transplantation (NODM) is now recognized as common immunosuppression-related complication[34] that is associated with an increased risk of graft loss, with the risk being comparable with that of acute rejection.[35] To date, few studies have examined the role of nonimmunosuppressive strategies (i.e., exercise and weight loss) prior to transplantation that may reduce the incidence of NODM after transplantation. Such strategies are needed because randomized studies of early steroid withdrawal have had little impact on NODM,[36] although a modest decrease in NODM was observed in patients randomized to receive cyclosporine rather than tacrolimus.[37]

With the increased choice of available maintenance immunosuppressive agents, individualization of immunosuppression, based not only on patient immunological risk but also cardiovascular risk, will be possible. Such strategies should be viewed as adjuncts to the early diagnosis and treatment of well-established cardiovascular risk factors. With the exception of dyslipidemia, direct evidence regarding the efficacy of cardiovascular risk reduction in transplant recipients is lacking and transplant clinicians must rely on extrapolation of information from nontransplant populations.

The level of kidney function achieved after transplantation has been associated with both patient and allograft survival and more recently with the development of hospitalized heart disease.[38,39] Because of these important associations, it is important that an accurate assessment of allograft function be made. A key component of CKD care in transplant recipients is recognition of the fact that patients who are typically thought of as having good graft function actually have significantly impaired kidney transplant function and are at risk for the complications of CKD. Serum creatinine

alone is not an accurate index of kidney function, and an estimate of the GFR is the preferred measure of kidney function. There are a number of prediction equations available to estimate kidney function in transplant recipients, and a review of the accuracy and limitations of these equations is beyond the scope of this discussion. The K/DOQI work group has recommended equations derived from the MDRD study for use in all adult patients with CKD.[3] The simplest of these formulas includes only four variables: Estimated GFR (ml/min/1.73 m^2) = 186 × Serum Creatinine$^{-1.154}$ × Age$^{-0.203}$ × 0.742 if female × 1.210 if African American.[2]

The level of kidney function achieved after transplantation is largely determined by donor and immunological factors. Because the mean level of kidney function established after transplantation is only 50 ml/min/1.73 m^2,[40] preservation of kidney function is an important aspect of CKD management in transplant recipients. Recent studies of administrative data sets and from the experience in single centers have described the change in kidney function after transplantation.[40–42] Of importance is the observation that transplant recipients have a mean rate of kidney function decline that is slower than that in patients with native kidney disease with similar levels of kidney function.[43] This is surprising given the fact that KTRs are at increased risk for kidney failure. Recent studies have shown secular improvements in the rate of kidney function decline after transplantation.[8,42] There is a need for further studies to identify the determinants of the change in kidney function after transplantation. It would appear that there are only relatively small differences in the rate of kidney function decline between the most commonly used maintenance immunosuppressive agents.[44] Surprisingly little direct information about the role of hypertension and proteinuria in kidney function decline in transplant recipients is available. These factors are known to accelerate the progression of kidney function decline in patients with native kidney disease. Similarly, the role of angiotensin-converting enzyme (ACE) inhibitors in preservation of kidney transplant function remains unclear, but is currently being investigated in a randomized control trial.[45] Evidence regarding the role of anemia in the progression of kidney function decline is relatively sparse.[46] Further studies to determine the optimal blood pressure and the role of proteinuria and other modifiable CKD factors, such as anemia, on the rate of kidney function decline after transplantation are needed. In the absence of direct evidence in the transplant population, it is reasonable to advocate treatment of these factors based on their established role in the progression of native kidney disease and because many of these factors also increase the risk of cardiovascular disease.

Chronic Kidney Disease Care in Patients with Allograft Failure

Despite the improvements in allografts survival, about one third of DD transplant recipients will suffer graft failure within the first 5 years of transplantation.[47] As such, it is appropriate for transplant physicians to consider the survival of patients after transplant failure as part of transplant related outcomes.

The survival of patients with transplant failure is known to be poor.[11,12,48] About 25% of patients in the United States who remain on dialysis after transplant failure die within 2 years of their return-to-dialysis date.[11] Some of these deaths may be preventable. For example, recent studies have demonstrated a higher rate of sepsis after dialysis initiation in transplant failure patients compared to nontransplant failure patients.[49] The role of continued immunosuppression or temporary vascular access was not specifically assessed but may have contributed to the higher rate of sepsis in the transplant failure group. Despite being known to physicians with knowledge of CKD, failed transplant recipients in the United States initiated dialysis with levels of hematocrit, albumin, erythropoietin use, and residual renal function that were suboptimal and similar to those in the general incident dialysis population.[50] These findings demonstrate that there are significant opportunities to improve the CKD management of transplant recipients and that there is a need for increased awareness of CKD among the medical professionals involved in the care of these patients.

Chronic Kidney Disease and Living Kidney Donors

The current CKD classification identifies chronic kidney disease when the GFR is less than 60 ml/min irrespective of the cause.[13] A number of studies have reported that the post-donation GFR of kidney donors may fall below this threshold.[51–53] Whether healthy individuals who develop a GFR less than 60 ml/min post kidney donation are at a similar risk of CKD-related complications as patients who develop a similar GFR through a disease process is not known. Recent studies have failed to show an increased risk of cardiovascular disease in kidney donors.[54] In the absence of evidence that kidney donors are at increased risk for adverse consequences, the inclusion of donors in the CKD classification should be considered an anomaly of the classification; it is to be hoped that it will be removed to avoid unintended consequences.

A full list of references are available at www.expertconsult.com.

Chapter 46

THE EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

Sushrut S. Waikar, M.D., M.P.H., and Jonathan Himmelfarb, M.D.

"The disease seems in general to come suddenly. The peculiar symptom is a sudden diminution of secretion of urine, which soon amounts to a complete suspension of it. The affliction is probably first considered as retention; but the catheter being employed, the bladder is found to be empty... after several days, the patient begins to talk incoherently, and shows a tendency to stupor. This increases gradually to perfect coma, which in a few days is fatal..." John Abercombie (1780-1828), "Observations on ischuria renalis."[1]

Acute kidney injury (AKI) is characterized by sudden (i.e., hours to days) impairment of kidney function. Descriptions of syndromes consistent with AKI date back to the ancient Greek period,[2] when the diagnosis was possible only by observing a reduction in urine volume. Initial descriptions of AKI from the early 20th century centered around specific conditions such as crush injuries,[3] war nephritis,[4] and falciparum malaria.[5] Sir William Osler in 1912 described several recognizable causes of AKI under the heading of "acute Bright's disease," including sepsis, pregnancy, burns, and toxins.[6]

The modern day conception of AKI has evolved alongside developments in pathology and clinical biochemistry, which have permitted clinicopathological correlations and earlier diagnosis.[7] AKI is not a single disease but rather a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in the blood urea nitrogen (BUN) concentration, an increase in the serum or plasma creatinine concentration, a reduction in urine volume, or some combination. The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction. In prerenal azotemia, glomerular filtration falls due to inadequate kidney perfusion from hypovolemia, decreased cardiac output, or renal vasoconstriction. Prerenal azotemia is considered to be functional in nature and reversible with restoration of renal perfusion. Intrinsic renal diseases can be subdivided into those affecting the glomeruli (e.g., glomerulonephritis), tubules (e.g., acute tubular necrosis), interstitium (e.g., acute interstitial nephritis), or blood vessels (e.g., thrombotic microangiopathy). Postrenal obstruction results from mechanical disturbance to the normal flow of urine from kidneys to ureter to bladder and finally to the urethra for elimination.

DEFINITION OF ACUTE KIDNEY INJURY

Until recently, a major obstacle to the study of AKI has been the absence of a standardized definition. The specific quantitative criteria for diagnosing AKI—as defined by a rise in serum creatinine (SCr) concentration—ranges widely in the published literature, with more than two dozen definitions in use. Recently, an international panel of experts in nephrology and critical care medicine proposed a consensus definition of AKI, termed the RIFLE criteria. AKI is stratified into three stages, *R*isk, *I*njury, and *F*ailure; the consequences of AKI are defined by the two last stages, *L*oss (i.e., need for renal replacement therapy) and *E*nd-stage renal disease. Each of the first three stages can be reached either by a rise in SCr or a reduction in urine output. The SCr criteria for

Risk, Injury, and Failure are a 50%, 100%, and 200% increase in SCr over baseline, respectively; "failure" can also be achieved by a greater than 0.5 mg/dL increase in SCr to at least 4 mg/dL. Another group, the Acute Kidney Injury Network (AKIN), has proposed a three-tiered definition of AKI that is essentially identical to R, I, and F, with the following exception: stage 1 AKI can be reached by an increase in SCr as small as 0.3 mg/dL over a 48 hour period. With the exception of the 0.3 mg/dL increase proposed by AKIN, the two definitions rely largely on percentage rises in SCr over baseline. Recently, Waikar and Bonventre[8] have suggested that the use of a percentage rise in SCr may be inappropriate, because of differences in creatinine kinetics in patients with chronic kidney disease, a common predisposing risk factor in the setting of AKI. Based on computerized simulations of creatinine kinetics, an alternative definition of AKI has been proposed that uses absolute increases in SCr over a 24 or 48 hour period to define AKI in three stages. The three definitions are compared in Table 46-1.

Several investigators have attempted to validate the prognostic significance of the RIFLE criteria in diverse clinical settings (reviewed by Ricci and associates[9]). Not unexpectedly, these studies have generally shown that increasing severity of AKI is associated with increasing risk of in-hospital mortality and other adverse outcomes. However, the relative merits of one creatinine-based definition over another, and the appropriate criteria by which to compare them, remain open questions.

There are several limitations of any SCr-based definition of AKI. First, the baseline SCr is often not known, making it impossible to gauge the absolute or percentage rise from baseline.[10] Second, creatinine itself is an inadequate biomarker of kidney injury because of tubular secretion, the need for steady state determinations for accurate estimates of glomerular filtration rate (GFR), and the confounding influences of muscle mass and changes in volume of distribution, the latter particularly in the setting of acute illness. Assessment of GFR by gold standards such as iothalamate or inulin clearance is cumbersome and impractical in the acute setting. In patients with prerenal azotemia, creatinine may rise in the absence of any structural injury to the kidneys. In patients with severe parenchymal kidney injury, such as lupus nephritis, SCr may not rise at all.

Recent investigation into tubular injury biomarkers may herald a paradigm shift in the definition AKI, similar to that seen over the past several decades in the definition of acute myocardial infarction (MI) (see Chapter 48). Acute MI is now defined on the basis of myocardial injury markers including troponin, without the requirement for a functional decrease in myocardial function such as cardiac output. It is possible that AKI may eventually be defined on the basis of sensitive injury biomarkers that rise well before the complex sequence of events before an ultimate reduction in GFR followed thereafter by a rise in SCr.

TABLE 46-1 Serum Creatinine-Based Definitions of Acute Kidney Injury

STUDY	DEFINITION
Acute Kidney Injury Network[88]	• Stage 1: increase of ≥ 0.3 mg/dL *or* 50% increase over baseline within 48 hr • Stage 2: ≥ 100% increase over baseline (doubling) • Stage 3: ≥ 200% increase over baseline *or* 0.5 mg/dL increase to at least 4 mg/dL
Acute Dialysis Quality Initiative[89*]	• RIFLE "R": ≥ 50% increase over baseline • RIFLE "I": ≥ 100% increase over baseline (doubling) • RIFLE "F": ≥ 200% increase over baseline *or* ≥ 0.5 mg/dL increase to at least 4 mg/dL
Contrast nephropathy[47]	• ≥ 0.5 mg/dL increase *or* 25% increase over baseline
Hou[11]	• Increase of ≥ 0.5 mg/dL if admission SCr ≤ 1.9 mg/dL • ≥1 mg/dL increase if admission SCr of 2 to 4.9 • ≥ 1.5 mg/dL increase if admission SCr > 5 mg/dL
Waikar and Bonventre[8]	• Stage 1: ≥ 0.3 mg/dL increase over 24 h *or* ≥ 0.5 mg/dL increase over 48 hr • Stage 2: ≥ 0.5 mg/dL increase over 24 h *or* ≥ 1 mg/dL increase over 48 hr • Stage 3: ≥ 1 mg/dL increase over 24 h *or* ≥ 1.5 mg/dL increase over 48 hr

*RIFLE categories *L* and *E* refer to "Loss" and "End-stage renal disease," respectively.

Early Cohort Studies of Acute Kidney Injury

Hou and colleagues in 1983 published one of the first chart-review based cohort studies of AKI.[11] These investigators focused on hospital-acquired disease and therefore excluded patients with established AKI on admission. Over a 5-month period beginning in 1978, a total of 2216 consecutive medical and surgical admissions to Tufts Medical Center in Boston were followed for the development of AKI. The definition of AKI in this study was based on an absolute increase in SCr depending on the admission SCr: increase in Scr of greater than 0.5 mg/dL if admission SCr was less than 1.9 mg/dL; increase of greater than 1 mg/dL for admission SCr of 2 to 4.9; or an increase of greater than 1.5 mg/dL for admission SCr of greater than 5 mg/dL. Overall, 4.9% of patients met criteria for AKI. The major causes of hospital-acquired AKI were decreased renal perfusion (42%), major surgery (18%), contrast nephropathy (12%), and aminoglycoside antibiotics (7%). The crude in-hospital mortality rate was 32%, and the degree of kidney injury as assessed by change in SCr was noted to be important. In-hospital mortality was 3.8% in patients with an increase in SCr of 0.5 to 0.9 mg/dL, and increased progressively to 75% in patients with a greater than 4 mg/dL increase who were not treated with renal replacement therapy. This study was also one of the first to establish the association between oliguria and mortality in patients with AKI (52% vs. 17% with and without oliguria, $p < 0.01$).

Shusterman and associates performed a case-control study of hospital-acquired AKI in patients admitted during 1 month to the Hospital of the University of Pennsylvania in Philadelphia in 1981.[12] The definition of AKI was different from that employed by Hou and associates 4 years earlier in the same journal. Acute kidney injury was defined as a greater than 0.9 mg/dL increase in SCr with baseline SCr of less than 2 mg/dL, or a greater than 1.5 mg/dL increase in SCr with baseline SCr of greater than 2 mg/dL; the incidence was 1.9% among patients on medical, surgical, and gynecological services. The 34 AKI cases were matched to 57 controls without AKI. From this small group of cases and controls, the authors found volume depletion, aminoglycoside use, septic shock, congestive heart failure, and

intravenous contrast administration as risk factors for AKI. They also found a 10-fold increased odds of death and a doubling of the length of stay among patients with AKI.

Nash, Hafeez, and Hou published a follow-up report of hospital-acquired AKI almost two decades later, using similar methodology and definitions to the earlier publication.[13] Over a 4-month period in 1996, they prospectively followed 4622 medical and surgical admissions at Rush Presbyterian-St. Luke's Medical Center in Chicago for the development of AKI, defined as in their earlier study. They identified 332 patients (7.2% of admissions) who developed AKI, higher than the 4.9% in the original study performed at a different institution. The in-hospital mortality rate of 19.4% was somewhat lower than the 25% reported previously. The most common causes of AKI remained decreased renal perfusion (39%; defined broadly to include congestive heart failure, cardiac arrest, and volume contraction), nephrotoxin administration (16%), contrast administration (11%), and major surgery (9%).

Multicenter Cohort Studies of Acute Kidney Injury

Initial cohort studies of AKI shed important light on the frequency, causes and mortality associated with hospital-acquired AKI. No matter how carefully conducted, single-center studies are inherently limited in terms of sample size and external validity (i.e., generalizability to AKI at other medical centers). Recognizing this limitation, and the heterogeneity of etiologies of AKI at individual institutions, investigators have conducted multicenter epidemiological investigations of AKI.

Liano and coworkers conducted a prospective, 9-month study of all AKI episodes in 13 tertiary-care hospitals in Madrid, Spain, beginning in 1991.[14] They defined AKI as a sudden rise in SCr of more than 2 mg/dL, excluding patients with preexisting chronic kidney disease, (CKD defined as SCr >3 mg/dL). Unlike the Hou[11] and Nash[13] studies, hospital- and community-acquired cases of AKI were included. Of the 748 episodes of AKI (representing 0.4% of admissions and 21 per 100,000 population), acute tubular necrosis (ATN) was the most frequent cause (45%, defined to include diverse causes including surgery, nephrotoxin administration, sepsis, and renal hypoperfusion), followed by prerenal azotemia (21%, defined as the rapid recovery of kidney function following volume administration or restoration of cardiac output), acute onset chronic renal failure (12.7%, not defined), and urinary tract obstruction (10%). The crude in-hospital mortality rate was 45% overall, and as high as 65.9% in patients requiring dialysis (which constituted 36% of all cases of AKI). In a follow-up study, Liano and colleagues provided more details on the specific differences between AKI in and outside of the intensive care unit (ICU).[15] Compared to non-ICU patients, those admitted to the ICU were younger, more likely to die in-hospital (71.5% vs. 31.5%), and more likely to have ATN from sepsis or renal hypoperfusion than nephrotoxin administration.

Brivet and colleagues focused on AKI occurring in the ICU in a 20-center, prospective, 6-month study performed in France in 1991.[16] They included all patients with a rise in SCr to at least 3.5 mg/dL and/or BUN to at least 100 mg/dL, or both, or a 100% increase if preexisting CKD. Patients with severe CKD (baseline SCr > 3.5 mg/dL) were excluded. Overall, 7% of ICU admissions developed AKI or had AKI on admission. The major causes of AKI were attributed to sepsis (48%), hemodynamic alterations (32%), nephrotoxin administration (20%), and prerenal factors (17%). Overall in-hospital mortality was 58% and was higher in those with sepsis (73%) and delayed occurrence of AKI after admission (71%). Another group of French investigators performed a similar prospective observational study beginning in 1996.[17] These authors found a 7.7% incidence of AKI in the ICU, defined as SCr of greater than 3.4 mg/dL or the need for dialysis.[17] Overall in-hospital mortality was 66%, and 81% in patients with AKI that developed 1 week after admission to the ICU.

The Program to Improve Care in Acute Renal Disease (PICARD) performed a 31-month-long, prospective observational cohort study of patients at five academic medical centers in the United States from 1999 to 2001.[18] Eligible patients were those in the ICU for whom nephrological consultation was obtained; AKI was defined as an increase in SCr of greater than 0.5 mg/dL if baseline was less than 1.5 mg/dL, or an increase of greater than 1 if baseline SCr was between 1.6 and 4.9. Unique to PICARD among AKI epidemiological studies to date was the extensive clinical detail captured (more than 800 data elements per patient, including details on dialysis procedures) and limited biological sample collection.

A total of 618 patients were enrolled in PICARD. One of the most illustrative findings in PICARD was the degree of heterogeneity of patients with AKI across the five medical centers in terms of baseline characteristics, processes of care, and in-hospital mortality. Even across five academic medical centers, in-hospital mortality associated with AKI from ATN and nephrotoxins ranged from a low of 24% to a high of 62%. Substantial differences in process of care were also evident across the five sites in terms of dialysis modality. Despite the many differences, however, the presumed etiologies of AKI were relatively similar among institutions. Fully 50% of patients were labeled as having ATN with no specified precipitant. The next most common etiologies included nephrotoxin administration (26%), cardiac disease (20%, including MI, cardiogenic shock, and congestive heart failure), ATN from hypotension (20%), ATN from sepsis (19%), unresolved prerenal factors (16%), and liver disease (11%). The PICARD cohort has been the subject of subsequent epidemiological studies to derive prediction rules for mortality[19] and to explore the associations between dialysis modality[20] and timing of initiation and survival.[21] The biological samples from subsets of PICARD participants have been used to study urea volume of distribution,[22] insulin resistance,[23] cytokine levels,[24] and oxidative stress[25] in patients with AKI.

The largest and most inclusive cohort study of AKI to date was conducted by the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators.[26] They prospectively studied patients admitted to 54 intensive care units across 23 countries over 15 months beginning in September 2000. The target population was patients with severe AKI: inclusion criteria were treatment with renal replacement therapy or AKI defined as oliguria

(<200 mL in 12 hours) or BUN of greater than 84 mg/dL. Of 29,269 patients admitted to the ICUs, 1738 (5.7%) had AKI. The most common causes of AKI were septic shock (47.5%), major surgery (34%), cardiogenic shock (27%), hypovolemia (26%), and nephrotoxin administration (19%) (multiple causes were allowed on the data collection form, accounting for total of more than100%).

The overall in-hospital mortality rate in the BEST Kidney cohort study was 60.2%. As with PICARD, mortality varied widely across centers. Among countries contributing more than 100 patients to the cohort, in-hospital mortality ranged from 50.5% to 76.8%. A multivariable logistic regression model to identify independent correlates of in-hospital mortality yielded several previously identified risk factors also found in PICARD[19] or the French Study Group,[16] or both, including delayed AKI, age, sepsis, and a generic disease severity score that included BUN and urine output. Follow-up studies from the BEST Kidney multinational database have compared severity scoring systems for AKI-related mortality[27] and investigated the relationship between diuretic administration and mortality.[28]

Large Database Studies of Acute Kidney Injury

Medical administrative and claims databases afford investigators the opportunity to study AKI in large numbers of patients over multiple years admitted to a wide spectrum of hospitals, including those not ordinarily represented in prospective cohort studies. The major limitation of most administrative databases is the lack of detailed clinical and laboratory information. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for acute renal failure (ARF) (584.x) and renal replacement therapies (39.95) have been shown to be accurate for the identification of patients with severe AKI (defined as AKI requiring dialysis, or AKI-D), but less accurate for AKI not requiring dialysis.[29]

Two studies to date have used large administrative or claims databases, or both, to study secular trends in the epidemiology of AKI in the United States. Xue and associates used inpatient claims data from a 5% sample of Medicare beneficiaries to investigate the incidence and mortality of ARF between 1992 and 2001.[30] Waikar and colleagues used the Nationwide Inpatient Sample (NIS), a nationally representative database of hospital discharges, to study AKI from 1988 and 2002.[31] Using the same ICD-9-CM codes to identify AKI and a similar and partially overlapping study population, the two studies found a marked rise in the incidence and fall in the mortality associated with AKI and AKI-D. Among Medicare beneficiaries, the incidence of AKI rose from 14 to 35 per 1000 discharges between 1992 and 2001; in the NIS, which unlike the Medicare database includes patients under the age of 65, the incidence of AKI rose from 4 to 21 per 1000 discharges between 1988 and 2002. Both studies showed a statistically significant decline in mortality, in contrast to the prevailing wisdom and a recent systematic review, which suggest that mortality rates have remained unchanged over decades.[32]

Liangos and associates used the National Hospital Discharge Survey (NHDS), a nationally representative hospital discharge database different from the NIS database used by Waikar and associates, to study AKI in patients admitted in 2001.[33] Using the same diagnosis codes, they reported that 19 per 1000 discharges had AKI, and that 21.3% died in-hospital, virtually identical to the findings in the NIS.

Both NIS and NHDS studies documented that patients with AKI have a median length of stay of 7 days, and that about one fourth are discharged to skilled nursing facilities. Costs attributable to AKI were not reported in the NIS, NHDS, or the Medicare analyses. Costs were addressed in a study by Fischer and colleagues involving administrative data from 23 Massachusetts hospitals.[34] They reported that uncomplicated AKI (i.e., excluding patients in the ICU) had the third highest median direct hospital costs ($2600) after acute MI and stroke.

The study from the NIS estimated the incidence of AKI at 288 per 100,000 United States population in 2002; the incidence of AKI-D was estimated to be 27 per 100,000 population. Other investigators have performed population-based epidemiology studies and estimated AKI-D rates of 45 per 100,000 (Manchester, UK),[35] 20 per 100,000 (Scotland),[36] and 8 per 100,000 (Australia).[37]

Hsu and coworkers used a large integrated administrative and laboratory database from Kaiser Permanente of Northern California to estimate the community-based incidence of AKI using SCr-based definitions rather than administrative codes, thereby avoiding a major limitation of the NIS, Medicare, and NHDS databases.[38] They confirmed the finding of a rising incidence of AKI over time: between 1996 and 2003, the incidence of AKI not requiring dialysis increased from 323 to 522 per 100,000, whereas the incidence of AKI-D increased from 20 to 30 per 100,000 (in keeping with the estimates from the nationally representative NIS study).[31]

A large integrated database, the Australian New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), has collected data on more than 600,000 adults admitted to 135 intensive care units since 1987. In addition to standard demographic, clinical, physiological, and laboratory data, investigators have extracted peak urea and SCr concentration and 24-hour urine output on the first day of admission. Analyses of secular trends in AKI from this large and comprehensive database have demonstrated a steady increase in AKI incidence of 2.8 percent per year, and a decrease in in-hospital mortality of −3.4% per year,[39,40] supporting the findings in U.S. administrative databases.

EPIDEMIOLOGY IN DISEASE-SPECIFIC STATES

Estimates of the incidence of AKI and associated mortality have been performed in numerous conditions, including sepsis, contrast nephropathy, major surgery, and nephrotoxic antibiotic administration. Several of the largest of studies are summarized in Table 46-2. A striking and consistent finding across all etiologies studied to date is the marked increase in mortality associated with the development of AKI.

TABLE 46-2 Incidence and Mortality of Acute Kidney Injury in Selected Conditions

AUTHOR, YEAR (REFERENCE)	SETTING	DEFINITION OF AKI	INCIDENCE	IN-HOSPITAL MORTALITY
Sepsis				
Bagshaw, 2008[40]	ICU admissions with sepsis (N=33,375)	Modification of RIFLE criteria, restricted to initial 24 hr of admission	AKI: 42.1% RIFLE "F": 9.6%	No AKI: 12.6% AKI: 29.7% RIFLE "F": 35.8%
Yegenaga, 2004[90]	ICU admissions with sepsis/SIRS (N=217)	SCr increase to > 2 mg/dL	AKI: 13% AKI-D: 6%	No AKI: 24 AKI: 72% AKI-D: 69%
Hoste, 2003[91]	Surgical ICU admissions with sepsis (N=185)	SCr rise from ≤ 1.0 to ≥ 2 mg/dL	AKI: 30% AKI-D: 11%	No AKI: 28% AKI: 57%
Neveu, 1996[92]	ICU admissions with AKI and sepsis (N=345)	100% increase in SCr to ≥ 3.5 mg/dL or BUN ≥ 100 mg/dL, or 100% increase in BUN or SCr	(Not reported; 46% of all AKI was in the setting of sepsis)	AKI from sepsis: 74% Non septic AKI: 45%
Rangel-Frausto, 1995[93]	ICU admissions with sepsis/SIRS (N=2527)	Acute SCr increase to > 2 mg/dL, need for dialysis, or doubling of SCr	AKI: 9% for SIRS, 51% for culture + septic shock	3% to 46%, depending on severity. AKI mortality not reported
Percutaneous coronary intervention				
Harjai, 2008[94]	PCI (N=985)	Increase in SCr > 0.5 mg/dL	AKI: 5.2% AKI-D: 0%	AKI: 40.9% No AKI: 10.2%
Marenzi, 2004[95]	ST-elevation AMI treated with primary PCI (N=208)	Increase in SCr > 0.5 mg/dL	AKI: 19% AKI-D: 3%	AKI: 31% No AKI: 0.6%
Mehran, 2004[47]	PCI (N=8357)	Increase in SCr ≥ 25% or ≥ 0.5 mg/dL	AKI: 13%	Not reported
Rihal, 2002[46]	PCI (N=7586)	Increase in SCr ≥ 0.5 mg/dL	AKI: 3.3% AKI-D: 0.3%	AKI: 22% No AKI: 1%
McCullough, 1997[96]	PCI (N=1826)	Increase in SCr > 25%	AKI: 14% AKI-D: 0.8%	No AKI: 1% AKI: 7% AKI-D: 36%
IV contrast for radiological examination				
Weisbord, 2008[45]	Baseline eGFR < 60, non emergent CT with IV contrast	Increase in SCr ≥ 25%	AKI: 6.5% AKI-D: 0%	30 day mortality no difference in AKI versus no AKI
Mitchell, 2007[97]	CT angiography to rule out pulmonary embolism in the emergency dept (N=1224)	Increase in SCr > 25% or 0.5 mg/dL within 7 days	AKI: 4% of entire cohort, 12% of those with 2 SCr measurements AKI-D: 0%	Not reported
Parfrey, 1989[98]	IV contrast for cardiac arteriography or CT examination (N=220)	Increase in SCr > 25%	AKI in +DM −CKD: 2.4% +DM+CKD: 8.8% −DM +CKD: 6.4%	Not reported
Cramer, 1985[99]	CT of the brain with (N=193) and without (N=233) IV contrast	Increase in SCr ≥ 50% to at least 1.2 mg/dL	AKI in IV contrast: 2.1% AKI no IV contrast: 1.3%	Not reported
Cardiac surgery				
Mehta, 2006[42]	Cardiac surgery (N=449,524)	Need for dialysis	AKI: not reported AKI-D: 1.4%	No AKI-D: 2.3% AKI-D: 43.6%
Brown, 2006[53]	Patients undergoing CABG (without valve replacement) N=1391	Increase in SCr < 25%, 25–49%, 50–99%, ≥ 100%	25–49%: 16% 50–99%: 7% ≥ 100%: 5%	(90 day mortality adjusted HR, ref = < 25% increase in SCr) 25%-49%: 1.8 50%-99%: 12.2 ≥ 100%: 5%: 30.8
Loef, 2005[55]	CABG or valvular surgery (N=843)	Increase in SCr ≥ 25% within 7 days of surgery	AKI: 17.2% AKI-D: 0.7%	No AKI: 1.1% AKI: 14.5% AKI-D: 83.3%
Thakar, 2005[100]	Open-heart surgery (N=18,838)	Need for dialysis	AKI: not reported AKI-D: 1.7%	Not reported
Bove, 2004[101]	Cardiopulmonary bypass/CABG (including valve replacement) (N=5068)	Increase in SCr ≥ 100%	AKI: 3.4% AKI-D: 1.9%	No AKI: 2.7% AKI: 46.2% AKI-D: 63.8%
Ryckwaert, 2002[102]	CABG or valvular surgery (N=591)	Increase in SCr ≥ 20% within 3 days of surgery	AKI: 15.6% AKI-D: 1.4%	No AKI: 1% AKI: 12% AKI-D: 37.5%

Continued

TABLE 46-2 Incidence and Mortality of Acute Kidney Injury in Selected Conditions—cont'd

AUTHOR, YEAR (REFERENCE)	SETTING	DEFINITION OF AKI	INCIDENCE	IN-HOSPITAL MORTALITY
Chertow, 1997[103]	CABG or valvular surgery (N=43,642)	Need for dialysis	AKI: not reported AKI-D: 1.1%	(30-day mortality) No AKI: 4.3% AKI: not reported AKI-D: 63.8%
Mangano, 1998[71]	CABG or valvular surgery (N=2222)	Increase in SCr of ≥ 0.7 mg/dL to at least 2 mg/dL	AKI: 7.7% AKI-D: 1.4%	No AKI: 0.9% AKI: 19% AKI-D: 63.8%
Nephrotoxic antibiotics				
Fowler, 2006[104]	Daptomycin (N=124) or gentamicin + penicillin or vancomycin (N=126)	Decrease in CrCl to < 50 mL/min, or decrease in CrCl of 10 mL/min if below 50 at baseline	AKI, daptomycin: 11% AKI, gentamicin: 26.3%	Not reported
Bates, 2001[105,106]	Amphotericin B (N=707))64 received liposomal preparation)	Increase in SCr of ≥ 50% to at least 2 mg/dL (severe: peak SCr at least 3 mg/dL)	AKI: 30% Severe AKI: 13%	No AKI: 14% AKI: 54%
Wingard, 1999[107]	Amphotericin B for aspergillosis (N=239)	Increase in SCr of ≥ 100%	AKI: 53% AKI-D: 14.5%	No AKI-D: 57% AKI-D: 76%
Leehey, 1993[108]	Aminoglycosides (N=243)	Increase in SCr of 0.5 mg/dL and 100% over baseline	AKI: 20.6% AKI-D: 1.2%	Not reported
Smith, 1980[109]	Gentamicin and tobramycin (N=146)		AKI: 19.2%	Not reported
Aortic aneurysm repair				
Prinssen, 2004[110]	Open (N=174) or endovascular (N=171) AAA repair	Increase in SCr ≥ 20%	AKI: 13% (both groups) AKI-D: not reported	Not reported
Ryckwaert, 2003[56]	Infrarenal aortic abdominal surgery (N=215)	Increase in SCr ≥ 20%	AKI: 20% AKI-D: 2.8%	No AKI:1.2% AKI: 9.3% AKI-D: 50%
Godet, 1997[111]	Thoracic or thoracoabdominal aortic surgery (N=475)	Increase in SCr to > 1.7 mg/dL or 30% over baseline	AKI: 25% AKI-D: 8%	AKI (no dialysis): 38% AKI-D: 56%

AAA, abdominal aortic aneurysm; *AKI*, acute kidney injury; *AKI-D*, acute kidney injury requiring dialysis; *AMI*, acute myocardial infarction; *BUN*, blood urea nitrogen; *CABG*, coronary artery bypass grafting; *CrCl*, creatinine clearance; *CKD*, chronic kidney disease; *CT*, computed tomography; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration; *HR*, hazard ratio; *ICU*, intensive care unit; *IV*, intravenous; *PCI*, percutaneous coronary intervention; *RIFLE*, Risk, Injury, Failure criteria for severity of acute kidney injury; *SCr*, serum creatinine; *SIRS*, systemic inflammatory response syndrome.

Risk Factors for the Development of Acute Kidney Injury

AKI that occurs in the hospital or outpatient setting can be predicted with limited accuracy. For AKI due to ischemic or toxic acute tubular necrosis, the severity of injury—e.g., duration of hypotension, dose, and/or duration of nephrotoxin exposure—are obvious risk factors for AKI. Specific predisposing demographic and clinical variables associated with a heightened risk of AKI have been investigated in a number of studies to help guide clinicians stratify patients according to the probability of AKI (Table 46-3).

Cardiac surgery has been the most extensively studied clinical setting for risk prediction of AKI. Cardiac surgery may cause AKI from a number of pathophysiological processes, including ischemia-reperfusion injury from hypotension, toxic injury from cardiopulmonary bypass-induced hemolysis with release of hemoglobin, inflammation, and oxidative stress.[41] The existence of large clinical databases from tens of thousands of patients undergoing cardiac surgery has enabled a number of detailed epidemiological studies of risk factors for AKI. The overall risk of AKI depends on the definition used; defined as a 25% increase in SCr, the risk is approximately 15%, while the risk of severe AKI requiring dialysis (AKI-D) is significantly lower, approximately 1% to 2%. Consistently observed risk factors for severe AKI include higher preoperative serum creatinine (or lower preoperative glomerular filtration rate), valve surgery, and diabetes mellitus. Scoring systems have been developed to assist clinicians to assign expected probabilities for AKI-D; the scoring systems have a moderate predictive ability, with C-statistics in the order of 0.8, meaning that the model has 80% probability of correctly identifying which of two randomly selected individuals developed AKI-D. The dominant risk factor in predicting AKI following cardiac surgery is preoperative kidney function. In scoring systems that assign points for various risk factors for AKI-D, preoperative SCr or estimated glomerular filtration rate (eGFR) are the highest weighted variables.[42,43] The association between preoperative eGFR and the risk of AKI-D is shown graphically in Figure 46-1. Beginning at eGFR below 60 mL/min/1.73 m^2, the risk of AKI-D increases sharply for lower eGFR.

AKI following noncardiac surgery has been less well-studied than cardiac surgery. Recent analyses of the National Surgical Quality Improvement Program (NSQIP) included 152,244 operations, 762 of which (1%) were complicated by AKI, defined as an increase in SCr of at least 2 mg/dL, or the need for dialysis.[44] Independent risk factors for AKI were age older than 56 years, male sex, emergency surgery, intraperitoneal surgery, diabetes mellitus, ascites,

TABLE 46-3 Predictors of the Development of Acute Kidney Injury

AUTHOR, YEAR (REFERENCE)	CLINICAL SETTING	N (% WITH AKI OUTCOME)	AKI DEFINITION	IDENTIFIED RISK FACTORS IN MULTIVARIABLE MODELS
Davidson, 1989[112]	Diagnostic cardiac catheterization	1162 (6%)	Increase in SCr ≥ 0.5 mg/dL	Older age and baseline SCr ≥ 1.2
Rich, 1990[113]	Cardiac catheterization, age ≥ 70, or older including percutaneous coronary intervention	183 (11%)	Increase in SCr ≥ 0.5 mg/dL	Contrast volume ≥ 200 mL, serum albumin < 3.5 mg/dL, DM, serum sodium < 135 mmol/L, SCr > 1.5, NYHA class III or IV
Lautin, 1991[114]	Femoral arteriography	394 (22%)	Increase in SCr > 0.3 mg/dL and 20% over baseline	Diabetes, baseline SCr > 1.5 mg/dL
McCullough, 1997[96]	Percutaneous coronary intervention	1826 (0.77%)	Need for dialysis	Lower baseline CrCl, diabetes, contrast volume
Gruberg, 2001[115]	Percutaneous coronary intervention	7690 (0.66%)	Need for dialysis	Non-Q-wave MI, saphenous vein graft intervention, peak postprocedural SCr, IABP, contrast volume, lower baseline CrCl
Rihal, 2002[46]	Percutaneous coronary intervention	7586 (3.3%)	Increase in SCr ≥ 0.5 mg/dL	Older age, higher baseline SCr, CHF, DM, shock, MI, PVD, contrast volume
Mehran, 2004[47]	Percutaneous coronary intervention	8357 (13.1%)	Increase in SCr ≥ 25% or ≥ 0.5 mg/dL	Hypotension, IABP, CHF, CKD, DM, age > 75, anemia, contrast volume
Marenzi, 2004[95]	Percutaneous coronary intervention for acute MI	208 (19%)	Increase in SCr > 0.5 mg/dL	Age ≥ 75, or older anterior acute MI, time-to-reperfusion ≥ 6 hrs, or longer contrast volume, IABP
Chertow, 1998[116]	Cardiac surgery	42,773 (1.1%)	Need for dialysis	Valve surgery, lower preoperative CrCl, IABP, prior heart surgery, NYHA class IV, PVD, LVEF < 35%, pulmonary rales, COPD, SBP ≥ 160 (CABG only)
Thakar, 2005[100]	Cardiac surgery	33,217 (1.7%)	Need for dialysis	Female, CHF, IABP, COPD, insulin-requiring diabetes, previous cardiac surgery, emergency/valve surgery, higher preoperative SCr
Mehta, 2006[42]	Cardiac surgery	449,524 (1.4%)	Need for dialysis	Higher preoperative SCr, older age, type of surgery (+/− valve), diabetes, recent MI, non-white race, chronic lung disease, prior CABG, NYHA class IV, cardiogenic shock
Wijeysundera, 2007[43]	Cardiac surgery	20,131 (1.3% to 2.2%)	Need for dialysis	Lower preoperative eGFR, diabetes, lower LVEF, previous cardiac surgery, procedure (+/− valve), urgency, and preoperative IABP
Kheterpal, 2009[44]	General surgery	75,952 (1%)	Need for dialysis	Age ≥ 56, or older male, emergency surgery, intraperitoneal surgery, DM, congestive heart failure, ascites, hypertension, CKD
Chawla, 2005[117]	Sepsis	194 (18%)	> 75% increase in SCr (baseline ≤ 2 mg/dL) or > 50% increase (baseline > 2 mg/dL)	Low serum albumin, high A-a gradient, active cancer
Hoste, 2003[91]	Sepsis	185 (16%)	Increase in SCr to at least 2 mg/dL	pH < 7.3 and SCr > 1 mg/dL on day of sepsis diagnosis
Yegenaga, 2004[90]	Sepsis	257 (11%)	Increase in SCr to at least 2 mg/dL or urine output < 400 mL/24 hr	Older age, higher SCr, higher CVP, serum bilirubin > 1.5 mg/dL
Chertow, 2006[19]	Established AKI	618 (64%)	Need for dialysis	Younger age, oliguria, higher BUN, liver failure
Chertow, 1998[118]	Established AKI (placebo arm of RCT)	256 (57%)	Need for dialysis or death	Oliguria, low serum albumin, acute MI, mechanical ventilation, arrhythmias
Godet, 1997[111]	Thoracoabdominal aortic surgery	475 (25%)	Increase in SCr to at least 1.7 mg/dL or ≥ 30% increase if preexisting CKD	Age > 50, preoperative SCr > 1.3, ischemia duration > 30 min, use of cell-saver, > 5 units pRBC transfusion
Bates, 2001[106]	Amphotericin B	643 (27%)	Increase in SCr ≥ 50% to at least 2 mg/dL	ICU stay at initiation of therapy, use of cyclosporine, maximum daily dose of amphotericin B

AKI, acute kidney injury; *A-a*, alveolar-arterial; *BUN*, blood urea nitrogen; *CABG*, coronary artery bypass grafting; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CrCl*, creatinine clearance; *CVP*, central venous pressure; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *IABP*, intraaortic balloon pump; *ICU*, intensive care unit; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *pRBC*, packed red blood cells; *PVD*, peripheral vascular disease; *RCT*, randomized controlled trial; *SBP*, systolic blood pressure; *SCr*, serum creatinine.

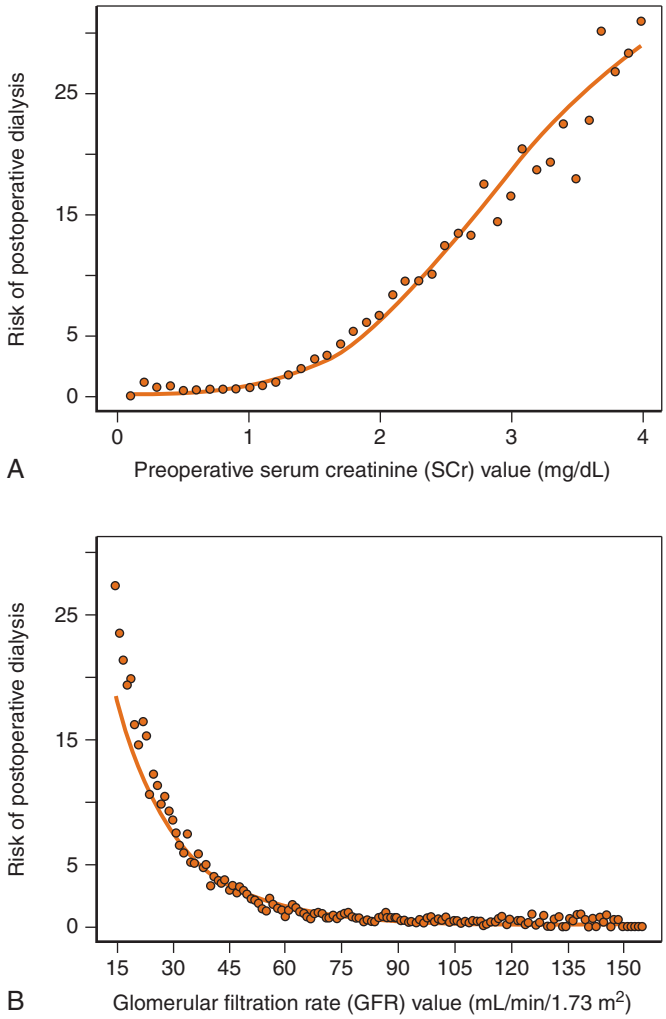


FIGURE 46-1 The risk of requiring postoperative dialysis according to preoperative serum creatinine concentration **(A)**, and preoperative estimated glomerular filtration rate **(B)**.

hypertension, and preoperative CKD. Similar to cardiac surgery scoring systems for AKI, the C statistic in this study was 0.8.

AKI following the administration of iodinated contrast material for radiological imaging or angiographic procedures (contrast-induced AKI [CI-AKI], or contrast nephropathy) is one of the most common forms of AKI in hospitalized individuals. The risk of CI-AKI depends greatly on the clinical context, with radiographic imaging constituting a significantly lower risk than angiographic imaging, due in part to the volume of administered contrast material. The incidence of CI-AKI following computed tomography is negligible for those with normal baseline renal function (eGFR > 60 mL/min/1.73 m^2). In a study of 421 patients with eGFR of less than 60 mL/min/1.73 m^2, Weisbord and coworkers[45] found an incidence of CI-AKI of 6.5% when defined as a greater than 25% increase in SCr, and only 0.5% when defined as a greater than 50% increase in SCr; no patient required postprocedure renal replacement therapy, and less than 1% of patients with baseline eGFR of greater than 45 mL/min/1.73 m^2 developed AKI. Risk factors for CI-AKI in this study included congestive heart failure, baseline SCr of greater than 1.5 mg/dL, and inpatient versus outpatient status.

Percutaneous coronary intervention (PCI) carries a significantly higher risk of CI-AKI than computed tomography with iodinated contrast. In 7586 patients undergoing PCI, Rihal and colleagues[46] found a 3.3% overall incidence of CI-AKI, defined as a greater than 0.5 mg/dL increase in SCr; the incidence was approximately 2.5% in those with baseline SCr of less than 2 mg/dL, 22.4% in those with baseline SCr between 2.1 and 2.9 mg/dL, and 30.6% in those with baseline SCr of greater than 3 mg/dL. Mehran and associates[47] derived a risk score to predict CI-AKI in a study of 8357 patients undergoing PCI: the eight variables that independently predicted the risk were hypotension, intraaortic balloon pump, congestive heart failure, CKD, diabetes, age older than 75 years, anemia, and volume of contrast.

Risk Factors for Mortality Associated with Acute Kidney Injury

An accurate scoring system for risk assessment in individuals with AKI would be of considerable use, given the high mortality rates associated with AKI and extremely high costs of care. Severity scores could assist in shared clinical decision making, monitoring of resource use, and comparison of the quality of care across institutions. A number of general illness severity scores have been developed for use in the critically ill hospitalized population. Validated scoring systems for critically ill patients, such as the Acute Physiologic and Chronic Health Evaluation (APACHE) system, the Simplified Acute Physiologic Score (SAPS), and the Mortality Prediction Model (MPM), have excellent calibration and discrimination, but perform less well in disease subpopulations such as AKI. Several disease-specific scoring systems have been developed for patients with AKI (Table 46-4). The most recent and comprehensive study was from the PICARD investigators, who enrolled 618 patients with AKI at five intensive care units in the United States. Chertow and associates developed predictive models in the PICARD cohort and compared them to 11 previously published scoring systems for mortality prediction in AKI.[19] They examined three clinically relevant time points: day of AKI diagnosis, day of nephrology consultation, and, for those with AKI requiring dialysis, the first procedure day. Age, sepsis, central nervous system failure, cardiovascular failure, liver failure, hematological failure, and the need for dialysis were the significant predictors of mortality in time-varying exposure models. Mortality prediction in patients with AKI remains imperfect: the models' areas under the receiver operating characteristics curve (AUC-ROC)—a test of diagnostic performance that ranges from 0.5 (no better than chance alone) to 1 (perfect prediction) and that represents the probability that a randomly selected individual who died will have a higher score than a randomly selected individual who survived—ranged from 0.5 to 0.73 in the PICARD cohort. A single-center study from Brazil[48] using a less strict definition for AKI (50% increase in SCr) examined the performance of five general and three AKI-specific

TABLE 46-4 Predictors of Mortality after Acute Kidney Injury

AUTHOR, YEAR (REFERENCE)	CLINICAL SETTING	N (% MORTALITY)	AKI DEFINITION	IDENTIFIED RISK FACTORS FOR MORTALITY IN MULTIVARIABLE MODELS
Liano, 1993[119]	Hospital	328 (53%)	Increase in SCr to at least 2.0 mg/dL (baseline < 1.5 mg/dL)	Coma, mechanical ventilation, hypotension, oliguria, jaundice, nephrotoxic etiology (protective), normal consciousness (protective)
Chertow, 1995[58]	Intensive care unit	132 (70%)	Need for dialysis	Mechanical ventilation, malignancy, nonrespiratory organ system failure
Neveu, 1996[92]	Intensive care unit	345 (59%)	Increase in SCr to at least 3.5 mg/dL or BUN to at least 100 mg/dL, or > 100% increase in SCr	Sepsis as cause of AKI, occurrence of AKI during ICU stay, oliguria, mechanical ventilation, generic severity of illness score, preadmission health status
Paganini, 1996[120]	Intensive care unit	512 (67%)	Need for dialysis	Male gender, mechanical ventilation, hematological dysfunction, bilirubin > 2.0 mg/dL, absence of surgery, higher SCr on first dialysis treatment, increasing number of failed organ systems, increased BUN from time of admission
Chertow, 1998[118]	Placebo arm of randomized controlled trial	256 (36%)	Increase in SCr of ≥ 1 mg/dL	Male gender, mechanical ventilation, oliguria, acute myocardial infarction, stroke/seizure, hypertension (protective), low serum bicarbonate
Metnitz, 2002[121]	Intensive care unit	839 (63%)	Need for dialysis	Mechanical ventilation, cardiopulmonary resuscitation, treatment of complicated metabolic acidosis/alkalosis, enteral nutrition (protective)
Mehta, 2002[122]	Intensive care unit	605 (52%)	BUN > 40 mg/dL or SCr ≥ 2 mg/dL; increase in SCr ≥ 1 mg/dL if preexisting CKD	Older age, male gender, nonrenal organ failure (respiratory, liver, and hematological), lower SCr, higher BUN, oliguria, higher heart rate
Lins, 2004[123]	Intensive care unit	293 (51%)	Increase in SCr to at least 2 mg/dL, or ≥ 50% increase in SCr if preexisting CKD	Older age, lower serum albumin, higher INR value, mechanical ventilation, CHF, higher serum bilirubin, sepsis, hypotension
Uchino, 2005[26]	Intensive care unit	1738 (60%)	BUN > 84 mg/dL or oliguria < 200 mL in 12 hours	Older age, delay between admission and inclusion into study, mechanical ventilation, generic severity of illness score, vasopressor use, metabolic diagnosis (protective), hematological diagnosis, septic shock, cardiogenic shock, hepatorenal syndrome
Chertow, 2006[19]	Intensive care unit	618 (37%)	Increase in SCr ≥ 0.5 or 1 mg/dL if baseline CKD	At diagnosis: older age, CKD stage 4 (protective), high BUN, liver failure, sepsis

AKI, acute kidney injury; *BUN*, blood urea nitrogen; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *ICU*, intensive care unit; *INR*, international normalized ratio; *SCr*, serum creatinine.

scoring systems in 366 patients, and found generally higher AUC-ROCs than in the multicenter PICARD cohort: on the day of nephrology consultation, the best performing general score was the Simplified Acute Physiology Score II (SAPS II) and the best performing AKI-specific score was the Stuivenberg Hospital Acute Renal Failure (SHARF) score, with AUC-ROCs of 0.83 and 0.81, respectively.

One of the first studies to examine the independent association between AKI and mortality showed that in patients undergoing radiocontrast procedures an increase in SCr of greater than 25% to at least 2 mg/dL was associated with a 5.5-fold higher odds of death, after adjustment for comorbid medical conditions.[49] Recent studies have explored whether the association between AKI and mortality extends to less severe kidney injury, as assessed by smaller increases in SCr. In a consecutive sample of 19,982 adults admitted to an urban medical center, Chertow and colleagues found that patients with an increase in SCr of just 0.3 to 0.4 mg/dL had a 70% higher multivariable-adjusted odds of death than patients with little or no change in SCr.[50] Other investigators have reported comparable findings in patients with congestive heart failure[51,52] and those undergoing cardiac surgery.[53–56] Brown and coworkers studied 1391 patients undergoing coronary artery bypass graft (CABG) surgery to investigate the prognostic significance of varying cutoffs for perioperative increases in SCr.[53] Compared to patients with less than 25% change in SCr, those with a 50% to 99% increase in SCr had a 6.6-fold increased risk of death at 90 days, adjusted for age and sex. These authors did not find a significant difference in mortality among patients with a 25% to 49% increase in SCr (hazard ratio [HR], 1.8; 95% CI, 0.73 to 4.44). In a study of more than 25,000 patients undergoing coronary angiography, Weisbord and associates found that small absolute increases in SCr of 0.25 to 0.5 mg/dL were associated with an increased odds of death of 83% (95% CI, 35% to 149%).[57]

Acute Kidney Injury in the Setting of Chronic Kidney Disease

It is intuitive that an already damaged organ is at heightened risk of acute injury. Indeed, elevated baseline SCr has been consistently observed to be a risk factor for the development of AKI in a number of settings, including radiocontrast administration, cardiac surgery, and sepsis (see Table 46-3).

Patients with CKD constitute a large fraction of patients with AKI in cohort studies. One third of patients in the PICARD cohort had CKD stage 4 or above.[19] Similarly, in the BEST cohort, 30% of patients had impaired kidney function (defined as "any abnormal serum level of creatinine or creatinine clearance prior to hospitalization") while 15% had unknown baseline kidney function.[26] In the cohort study by Nash, 151 of 332 patients with AKI had SCr concentrations of greater than 1.2 at baseline.[13] Interestingly, patients with CKD have been reported in some studies to have lower in-hospital mortality than patients without CKD who develop AKI. This finding has been noted in large database studies and studies to identify predictors of mortality following AKI. For example, among patients included in the NIS, 22% of patients with CKD and AKI-D died in-hospital, compared to 30% of patients without CKD.[31] In the PICARD cohort, baseline CKD conferred a 43% (95% CI, 16% to 61%) lower adjusted odds of in-hospital mortality[19]; CKD was not associated with lower mortality in the BEST-Kidney cohort.[26] Used as a continuous variable, higher baseline SCr has also been associated with lower mortality in studies examining outcomes following AKI.[19,58] Reasons that may underlie this seemingly paradoxical finding include confounding by malnutrition (and lower SCr values from low muscle mass), and unrecorded differences in disease severity between those with and without CKD who develop AKI. The latter may reflect relatively less severe kidney injury required in patients with CKD to manifest AKI, as currently diagnosed.

The presence or absence of CKD probably influences long-term outcome in survivors of AKI-D. In a population-based surveillance study of AKI from Calgary, among all patients with AKI who required maintenance dialysis 1 year following hospital admission, 63% had preexisting CKD (median baseline SCr 2.6 mg/dL).[59] Because the presence of CKD influences the risk of AKI, its consequences, and the propensity for the development of end-stage renal disease (ESRD), future studies of AKI epidemiology should use definitions that incorporate baseline CKD stage, as has been suggested by others.[60,61] Likewise, prevention and intervention studies of AKI should be stratified on baseline kidney function.

Long-Term Implications of an Episode of Acute Kidney Injury

Parikh and associates studied the long-term risk of death conferred by an episode of AKI in more than 140,000 elderly patients admitted for acute MI,[62] and found a graded association between the severity of AKI and death up to 10 years following discharge. Compared to those who did not suffer an episode of AKI, the multivariable-adjusted risk of death at 10 years was increased by 15% after mild AKI, 23% after moderate AKI, and 33% after severe AKI (Figure 46-2). A systematic review and metaanalysis by Coca and colleagues of 48 studies that reported long-term outcomes after AKI confirmed the association between AKI and long-term mortality.[63]

The kidney possesses a remarkable capacity for repair after even severe insults sufficient to cause temporary dialysis dependence.[64] The classic teaching has been that the kidneys recover completely after an episode of AKI due to acute tubular necrosis. However, even complete recovery to baseline as inferred by the SCr concentration may mask permanent structural damage to kidney parenchyma. Animal studies of AKI have shown permanent damage to the microvasculature and the development of tubulointerstitial fibrosis in kidneys that apparently recovered completely from ischemia-reperfusion injury.[65,66] Episodes of AKI may therefore predispose to worsening hypertension, proteinuria, and steeper decline in GFR in survivors of the initial episode.

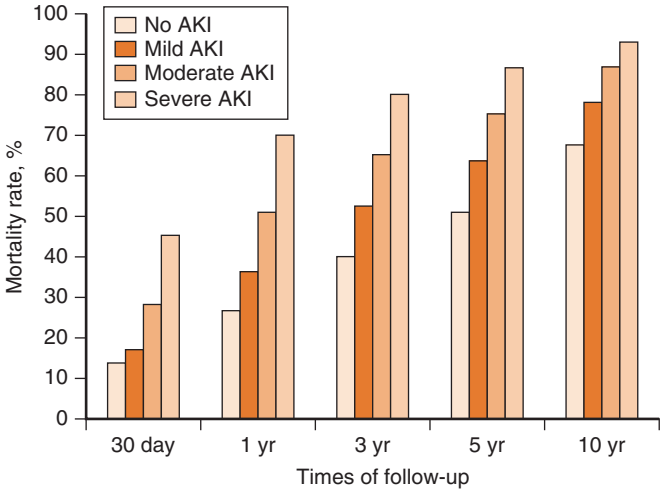


FIGURE 46-2 The risk of in-hospital and long-term mortality following an episode of acute kidney injury, by severity of injury. AKI, acute kidney injury. (Modified from C.R. Parikh, S.G. Coca, Y. Wang, et al., Long-term prognosis of acute kidney injury after acute myocardial infarction, Arch. Intern. Med. 168 [9] [2008] 987–995.)

The large study by Hsu and associates using the Kaiser Permanente of Northern California database sheds light on the long-term risks of renal function decline after an episode of AKI.[67] The investigators tracked more than 39,000 hospitalized individuals with preexisting CKD and examined long-term outcomes in those who did and did not suffer an episode of superimposed AKI. They found that superimposed AKI led to a 30% higher risk of death or ESRD during long-term follow-up of up to 7 years. Another study from the Kaiser Permanente Database examined long-term outcomes of severe AKI requiring dialysis in patients with previously normal or near-normal baseline renal function: Lo and coworkers found that an episode of AKI requiring dialysis conferred a striking 28-fold increased risk of progressive CKD and a more than twofold increase in the risk of death.[68] Ishani and associates found in a large administrative database study of Medicare beneficiaries that both AKI and CKD (individually and together) were strong predictors for the subsequent development of ESRD.[69]

COSTS ASSOCIATED WITH ACUTE KIDNEY INJURY

Because AKI is a major and potentially fatal complication in hospitalized individuals, it is not surprising that associated costs are greatly increased. Chertow and colleagues found that the multivariable-adjusted marginal costs of

hospitalization were increased by nearly $5000 after an increase in SCr of more than only 0.3 mg/dL.[50] Using RIFLE criteria "R" to define AKI, Dasta and associates showed that postoperative costs following CABG surgery were increased by more than 60% when AKI occurred.[70] The overall annual additional expenses due to AKI following cardiac surgery have been estimated at several hundreds of millions of dollars.[71,72] Extrapolating from estimates from a teaching hospital in Boston, Chertow and associates estimated that overall health care expenditures attributable to hospital-acquired AKI may exceed $10 billion annually.[50]

ACUTE KIDNEY INJURY IN THE DEVELOPING WORLD

The epidemiology of AKI differs tremendously between developed and developing countries, because of differences in demographics, economics, geography, and comorbid disease burden.[73] While certain features of AKI are common to both—particularly since urban centers of some developing countries increasingly resemble those in the developed world—many etiologies for AKI are region-specific, such as envenomations from snakes,[74–77] spiders,[78] caterpillars,[79] and bees;[80,81] infectious causes such as malaria[82] and leptospirosis;[83] and crush injuries and resultant rhabdomyolysis from earthquakes.[84–87]

SUMMARY

AKI is an increasingly common and potentially catastrophic complication in hospitalized patients. Our understanding of the incidence and consequences of AKI has grown considerably, yet mortality rates remain unacceptably high despite significant advances in the care of the critically ill. CKD is a dominant risk factor for AKI, and AKI may contribute to progressive CKD. The rising incidence of AKI and CKD, and their strong associations with poor clinical outcomes, highlight the need for kidney disease prevention and treatment as major public health priorities.

A full list of references are available at www.expertconsult.com.

Chapter 47

METABOLIC AND NUTRITIONAL COMPLICATIONS OF ACUTE KIDNEY INJURY

Edward D. Siew, M.D., M.S.C.I., and Jonathan Himmelfarb, M.D.

Despite advances in the provision of hospitalized care, acute kidney injury (AKI) remains common and tightly associated with disappointingly high mortality rates.[1–3] Depending on the definition applied and population studied, between 5% and 25% of hospitalized patients are afflicted, with observational and healthcare data suggesting an increasing disease incidence.[2,4] Among severe cases, patients with AKI present at minimum a complicated array of challenges detailed by the extent of the underlying precipitant, the scope of the systemic inflammatory and oxidative stress responses, and specific metabolic derangements resulting from the kidney injury itself and its subsequent therapies. As these complications represent profound hindrances to recovery, it is perhaps of little surprise that mortality in this patient population often exceeds 60%.[3,5]

While studies examining predictors of poor outcome frequently list factors reflecting comorbidity burden and illness severity, the nutritional status of patients with AKI is often also impaired representing an important determinant of morbidity and mortality. In addition to imbalances in electrolyte, acid-base, and volumes status, AKI also induces alterations in protein, carbohydrate, and lipid metabolism.[6] The extent of these abnormalities and the processes that drive them adversely impact the nutritional and metabolic status of patients with AKI. This chapter will provide an overview of these complications, including discussions of the key perturbations observed in substrate and energy metabolism, the underlying pathophysiological mechanisms, and the debates surrounding the provision of nutritional and metabolic support in this high-risk population.

TERMINOLOGY

Similar to AKI itself, a variety of historical definitions have been applied to describe the impaired nutritional status observed in acute and chronic kidney diseases including uremic wasting, renal cachexia, kidney disease wasting, malnutrition-inflammation complex, and protein-energy malnutrition. This heterogeneity has resulted in been the potential for misinterpretation of the available literature and of fundamental concepts. For example, while applied liberally, the term "*malnutrition*" refers specifically to a collection of findings resulting from inadequate nutrient and caloric intake *reversible* upon adequate replenishment. While similar abnormalities also are observed in a variety of disease processes, their tendency to persist despite provision of nutritional supplementation makes them distinct from simple malnutrition (Table 47-1).[7] An illustrative example is serum albumin, a classic biochemical marker of nutritional status. While relatively preserved during starvation until near death, significant decrements in this biomarker are noted relatively early and throughout the course of several disease processes, despite nutritional resuscitation.[8,9] Investigations directed towards explaining these apparent defects in nutrient utilization and enhanced catabolic responses have yielded several

TABLE 47-1 Common Nutritional Features in Patients with Malnutrition versus Catabolic Disease Processes

FEATURES	MALNUTRITION	CATABOLIC DISEASE STATE
Appetite	Starving	Anorectic
Metabolic rate	Decreases adaptively	Remains the same or increases
Principal substrate	Lipids/fatty acids	Lean body mass/muscle
Serum albumin	Preserved early	Depressed early
Response to nutrition	Effective	????

potential culprits. Among these are factors relating to both the determinants of AKI, and its downstream complications including inflammation, oxidative stress, acidemia, uremic toxin accumulation, dialytic losses, and insulin resistance (Figure 47-1).[10]

Recognizing the need for a consensus definition incorporating these latter elements, the International Society of Renal Nutrition and Metabolism (ISRNM) recently proposed the consensus term *protein-energy wasting* (PEW) to characterize the generic loss of lean body mass and fuel reserves where diminished intake is only one of several possible contributors.[10] Their goal was to provide a systematic definition to serve as a standard for future researchers and clinicians alike and to clarify misconceptions in terminology. Minimum requirements to meet this diagnosis include deficiencies in biochemical parameters (albumin, prealbumin, or cholesterol), anthropomorphic measures (body mass index [BMI] < 23 or unintentional weight loss), quantified muscle mass muscle mass (assessed by creatinine appearance, bioimpedance analysis [BIA], or midarm muscle circumference), and low dietary protein/energy intake (<0.6 g/kg/day in patients with the National Kidney Foundation's chronic kidney disease [CKD] stages 2 to 5, for example) (Table 47-2).[10] These criteria remain to be validated in both community-acquired and hospital-acquired AKI.

Prevalence of Protein-Energy Wasting in Acute Kidney Injury

Observational studies of patients with AKI have found PEW to be highly prevalent at the time of disease presentation with ongoing risk during the course of hospitalization. Fiaccadori and coworkers studied 309 patients with AKI admitted to a renal intermediate care unit and observed severe preexisting malnutrition, defined by Subjective Global Assessment (SGA), in 42% of patients with AKI.[11] Affected patients experienced a higher likelihood of in-hospital death, complications, and healthcare resource utilization. Another study of 100 retrospectively identified AKI patients demonstrated that hypoalbuminemia (3.5 g/dl) and hypocholesterolemia (<150 mg/dl) on hospital admission were independently predictive

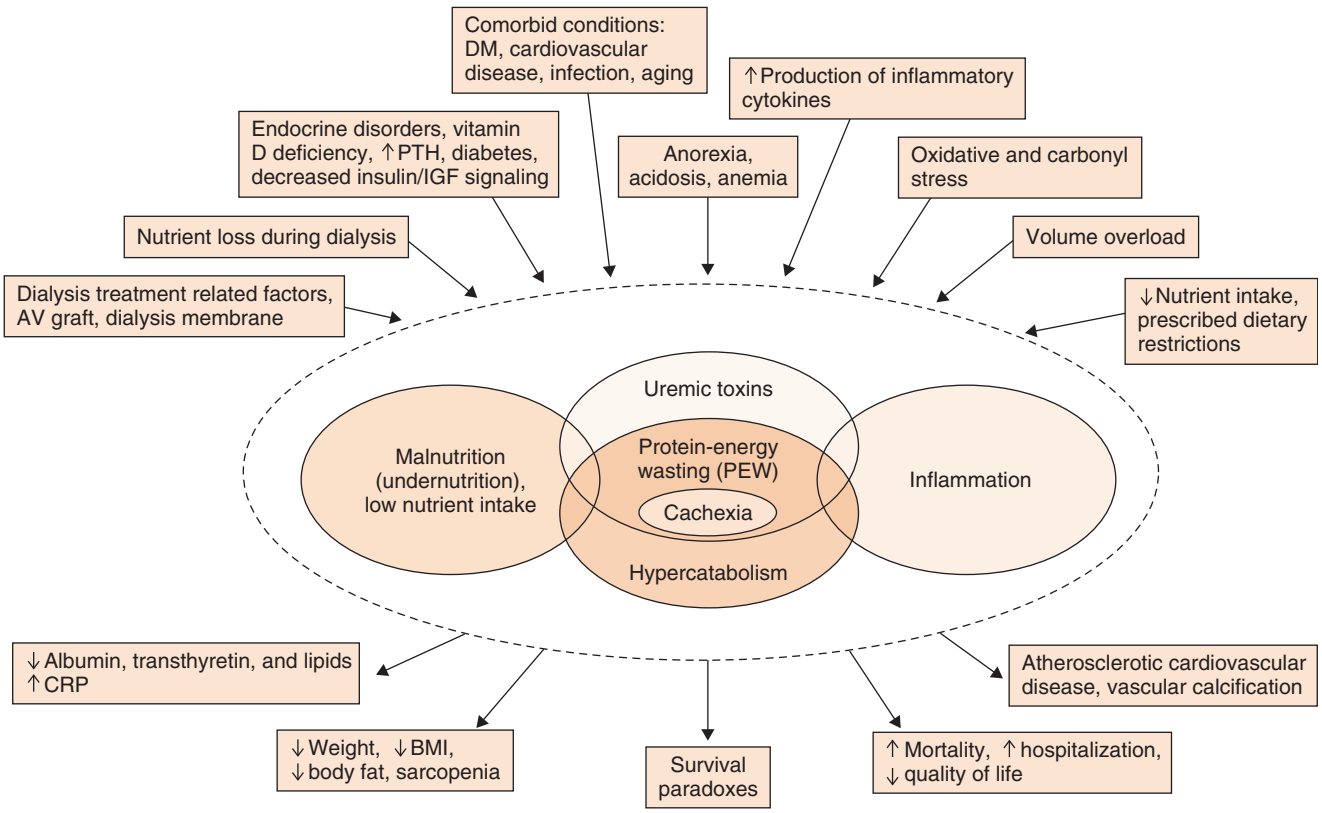


FIGURE 47-1 Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease. *AV*, atrioventricular; *BMI*, body mass index; *CRP*, C-reactive protein; *DM*, diabetes mellitus; *IGF*, insulin like growth factor; *PTH*, parathyroid hormone. (Reprinted with permission from Macmillan Publishers Ltd: D. Fouque, K. Kalantar-Zadeh, J. Kopple, et al., A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease, Kidney Int. 73 [4] [2008] 391-398.)

of mortality.[12] While patients admitted to a general medical service often develop PEW during the course of hospitalization and are at risk for increased hospital stay and mortality studies have examined the association between nutritional status and outcomes in AKI specifically.[13] However, recent longitudinal study of prealbumin levels in 161 patients with AKI requiring renal consultation observed that low serum prealbumin (<11 mg/dl) independently predicted in-hospital mortality after adjustment for severity of illness, RIFLE class, and AKI treatment.[14] Further, every 5 mg/dl increase in prealbumin level was associated with an additional 29% decrease in hospital mortality (hazard ratio [HR] 0.71; 95% CI, 0.52 to 0.96), suggesting its potential as a prognostic marker. Whether prealbumin and other plasma nutritional markers reflect recent nutritional status or are governed by the extent of underlying inflammation and illness severity has not been elucidated. More importantly, whether treatment or prevention of PEW, impact outcomes in AKI remains an important issue being addressed.

Dysmetabolism of Acute Kidney Injury

Acute illness often has a significant impact on a patient's metabolic milieu, which is further compounded by loss of kidney homeostatic function in AKI. Included among these alterations is dysregulation of the host inflammatory response and enhanced oxidative stress. In concert and in isolation, both have been implicated in the development and consequences of AKI and associated with derangements in carbohydrate, lipid, and protein metabolism (Figure 47-2).

Inflammation

Since AKI rarely occurs in isolation, the inflammation which accompanies it, is often described in the context of the acute physiological disturbance in which it coexists. Severe illness of almost any etiology is associated with a generalized host inflammatory response, referred to as the systemic inflammatory response syndrome (SIRS).[15] Key responses to tissue injury or infection include the elaboration of potent inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and compensatory antiinflammatory response (CARS) mediators such as IL-10 into the systemic circulation.[16] While critical to the modulation of immunity and cellular repair, imbalances of these responses have been postulated to disrupt capillary permeability, endothelial and vasomotor function, and coagulant and complement cascades.[16] When sustained, these imbalances also adversely affect the prognosis of this patient population likely via contribution to the development of multiple organ dysfunction syndrome (MODS).[17,18]

The kidneys appear particularly susceptible to the effects of dysregulated inflammation, making it of little surprise that sepsis remains one of the most potent determinants of the onset and prognosis of AKI.[5,19] Infusion of TNF-α and IL-1 in animal models produces renal injury by promoting local neutrophil adhesion and activation and decrements in renal blood flow via effects on nitric oxide (NO) and prostaglandin synthesis.[20,21] The extension of these findings to humans have been described by repeated observations detailing how a proinflammatory phenotype confers high risk for the development of AKI. Chawla and coworkers, for example, recently demonstrated an independent association between elevations in plasma IL-6 levels and the development of AKI in a cohort of critically ill patients with severe sepsis.[22] Similarly, in examining the ability of inflammatory cytokines to predict AKI in 876 patients with acute respiratory distress syndrome(ARDS), Liu and associates found elevations of IL-6, soluble TNF receptors, and plasminogen activator inhibitor-1 (PAI-1) to be predictive of AKI even after adjusting for age, demographics, intervention, and severity of illness.[23]

In addition to contributing to AKI development, dysregulation of inflammatory and immune responses may be further impaired in patients with established AKI. In a subset of patients from the multicenter Program to Improve Care in Acute Renal Disease (PICARD) study, the association between serum cytokine levels and outcome was compared

TABLE 47-2 Proposed Criteria for the Diagnosis of Protein-Energy Wasting Syndrome in Acute Kidney Injury or Chronic Kidney Disease

CRITERIA
Serum Chemistry
Serum albumin <3.8 g per 100 ml (Bromcresol Green)[a]
Serum prealbumin (transthyretin) <30 mg per 100 ml (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2-5)[a]
Serum cholesterol <100 mg per 100 ml[a]
Body mass
BMI <23[b]
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
Total body fat percentage <10%
Muscle mass
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
Reduced midarm muscle circumference area[c] (reduction >10% in relation to 50th percentile of reference population)
Creatinine appearance[d]
Dietary intake
Unintentional low DPI <0.8 g kg^{-1} day^{-1} for at least 2 months[e] for dialysis patients or <0.6 g kg^{-1} day^{-1} for patients with CKD stages 2-5
Unintentional low DEI <25 kcal kg^{-1} day^{-1} for at least 2 months[e]

(Reprinted by permission from Macmillan publishers Ltd: D. Fouque, K. Kalantar-Zadeh, J. Kopple, et al., A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease, Kidney Int. 73 [4] [2008] 391-398.)

[a]Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines.

[b]A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, postdialysis dry weight. See text for the discussion about the BMI of the healthy population.

[c]Measurement must be performed by a trained anthropometrist.

[d]Creatinine appearance is influenced by both muscle mass and meat intake.

[e]Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.

AKI, acute kidney injury; *BMI*, body mass index; *CKD*, chronic kidney disease; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *GFR*, glomerular filtration rate; *nPCR*, normalized protein catabolic rate; *nPHA*, normalized protein nitrogen appearance; *PEW*, protein-energy wasting.

At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2-4 weeks apart.

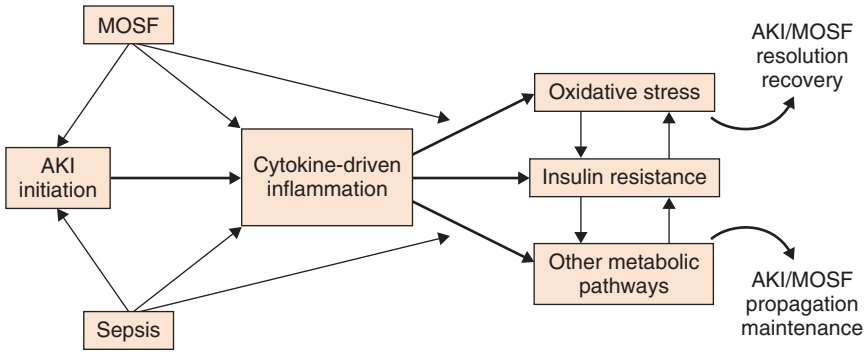


FIGURE 47-2 A proposed mechanistic approach to dysmetabolism of AKI. The dysmetabolism of acute illness is exacerbated in AKI owing to loss of kidney homeostatic function. Once established, these metabolic derangements, along with other potential pathways including but not limited to endothelial dysfunction, interact with each other to the extent that they may be the decisive factor leading to recovery or death. On the other hand, they also represent intriguing targets for future intervention in patients with AKI. *AKI*, acute kidney injury; *MOSF*, multisystem organ failure. (Reprinted with permission from Macmillan Publishers Ltd: J. Himmelfarb, T.A. Ikizler, Acute kidney injury: changing lexicography, definitions, and epidemiology. Kidney Int. 71 [10] [2007] 971-976.)

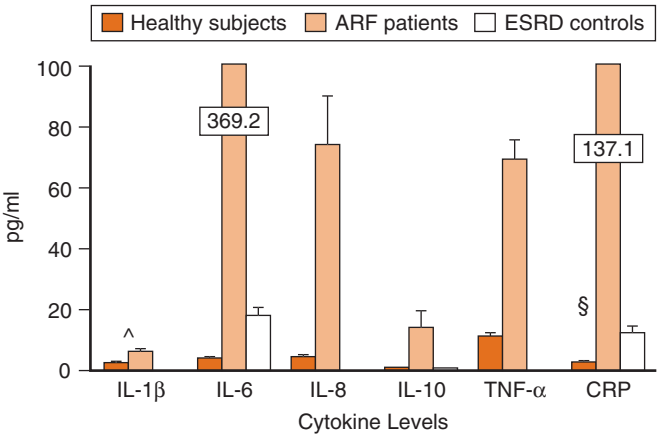


FIGURE 47-3 Cytokine levels of critically-ill patients with acute kidney injury at the time of nephrology consultation compared to healthy subjects or those with ESRD on chronic hemodialysis. Bars and error bars represent mean ± SEM for each time point. $P = 0.031$ for interleukin (IL)-1β (AKI study patients vs. healthy subjects); $P < 0.001$ for all other comparisons (AKI study patients vs. healthy subjects and AKI study patients vs. ESRD control patients). §CRP in mg/l. *AKI*, acute kidney injury; *ARF*, acute renal failure; *CRP*, C-reactive protein; *ESRD*, end-stage renal disease; *IL*, interleukin; *TNF-α*, tumor necrosis factor α; (Reprinted with permission from Macmillan Publishers Ltd: E.M. Simmons, J. Himmelfarb, M.T. Sezer, et al., Plasma cytokine levels predict mortality in patients with acute renal failure, Kidney Int. 65 [4] [2004] 1357-1365.)

in critically ill patients with AKI at the time of nephrology consultation.[24] Relative to healthy controls and patients on chronic hemodialysis, AKI patients experienced a 10- to 20-fold elevation in several proinflammatory cytokines including IL-6, IL-18, TNF-α, C-reactive protein (CRP), and the antiinflammatory cytokine IL-10 (Figure 47-3). Interestingly, these elevations were observed in AKI patients both with and without evidence of sepsis. Elevations of IL-6 and IL-8 also appeared to independently predict in-hospital mortality. Acknowledging the simultaneous elevation of the anti-inflammatory cytokine IL-10, the same group of investigators examined the effect of the systemic cytokine profile on immune function at the cellular level. Lipopolysaccharide (LPS) stimulation of monocytes from AKI patients was met with a decreased ability to augment production of IL-1β, TNF-α, and IL-6 compared to CKD and end-stage renal disease (ESRD) patients.[25] This suggests that imbalances in inflammation and immune responses in AKI represent a complex interplay at both a local and systemic level and involve more than just a simple overproduction of proinflammatory cytokines on a systemic level as traditionally believed.

Abundant evidence implicates a critical role for local inflammation and leukocyte infiltration in the pathogenesis of AKI due to multiple insults including sepsis,[19,26] ischemia-reperfusion,[27,28] and nephrotoxic injury.[29] While detailing these mechanisms is beyond the scope of this chapter, it is worth noting that the contribution of AKI to systemic inflammation and its subsequent effects on distant organ function is an area of active investigation. Several animal models have demonstrated systemic release of inflammatory markers including, but not limited to, TNF-α, IL-1β, CRP, and IL-12 after experimentally induced ischemia-reperfusion injury.[30–33] Ischemia-induced AKI has recently been shown to result in a rapid increase in serum CRP and granulocyte colony-stimulating factor (G-CSF) levels and inflammatory and functional changes in the brain not seen with ischemic liver injury. More recently, bilateral nephrectomy has been used in animals as a model of acute renal loss not confounded by the systemic effects of ischemic injury.[32] Hoke and colleagues demonstrated a statistically significant increase in circulating levels of IL-6 and IL-1β after bilateral nephrectomy that was independently associated with an inflammatory injury in the pulmonary architecture.[32] Finally, a recent analysis of genomic changes in the kidney and lung after ischemic AKI detected similar upregulation in the transcription of several genes responsible for inflammation and innate immunity in both organs. Functional genomic analysis suggested that increased signaling at the level of IL-6 and IL-10 might be responsible for these remote effects.[34]

In summary, dysregulated expression of pro- and anti-inflammatory mediators is a central component to both the development of AKI and its consequences at a local and systemic level. The biological effects of these mediators can be extensive, impacting both distant organ function and the capacity to effectively use nutritional substrates.

Oxidative Stress

During normal physiological conditions, cellular metabolism results in the continuous formation of reactive oxygen species, primarily through mitochondrial oxidative phosphorylation. This phenomenon is counterbalanced by the detoxification and decomposition of reactive oxygen species (ROS) via endogenous antioxidant compounds. In a number of pathological states, increased oxidative stress can occur when an imbalance develops between oxidant production and

antioxidant defense. Antioxidants are a varied group of molecules with diverse functions. These include enzymes with specific catalytic properties, water and lipid soluble chemical moieties with relatively nonspecific scavenging capacity, and metal chelating agents, which can inhibit oxidant production. As a rule, antioxidants control the prevailing relationship between reducing and oxidizing (redox) conditions and biological systems. Once regarded as virtually a medical curiosity, a large body of evidence now implicates reactive oxygen species as important mediators of ischemic and toxic tissue injury.

Considerable experimental data point to increased oxidative stress as a contributor to renal tubular epithelial cell injury and resultant AKI.[35] The dysregulated inflammatory response increases oxidative stress in patients with AKI. Furthermore, since uremia has now been unequivocally established as an increased oxidative stress state, the resulting loss of kidney function in AKI may exacerbate systemic oxidative stress.[36] Finally, increased systemic oxidative stress may contribute to the development and maintenance of the MODS, thereby directly contributing to adverse outcomes in critically ill patients with AKI. Available data points to a critical role for increased oxidative stress in the pathogenesis of complications related to AKI.

What is Oxidative Stress?

Oxidative stress is often defined as a disturbance in the balance between oxidant production and antioxidant defense. An imbalance in favor of prooxidants can lead to the oxidation of macromolecules, thereby resulting in tissue injury. Oxidative processes predominantly occur within the mitochondria, and the mitochondrial cytochrome oxidase enzyme complex accounts for the majority of metabolized oxygen. The cytochrome oxidase enzyme complex transfers four electrons to oxygen in a coordinated reaction, producing two molecules of water as a byproduct. The mitochondrial cytochrome enzyme complex contains four redox centers, each of which stores a single electron.

Mechanisms for the simultaneous reduction of the four redox centers resulting in the transfer of electrons are evolutionarily conserved and limit the production of reactive oxygen species. Nonetheless, mitochondrial oxygen can leak through the electron transport chain, resulting in the formation of reactive oxygen intermediates and free radicals, which can then diffuse out of the mitochondria and be a source of oxidative stress.

An additional important in vivo source of excess oxidants occurs through the action of another enzyme complex, nicotinamide adenine dinucleotide phosphate, (NADPH) oxidase.[37] The NADPH oxidase system also is highly conserved and is the sole enzyme system that deliberately produces ROS, primarily to influence cell signaling events. The NADPH oxidase is particularly important within the endothelium and in phagocytic cells for the generation of reactive oxygen intermediates. During an inflammatory response, phagocytes consume high levels of oxygen for the generation of reactive oxygen intermediates as part of the host defense against pathogens via the respiratory burst. Phagocytes contain other enzymes (including superoxide dismutase, NO synthase, and myeloperoxidase), which also contribute to the production of hydrogen peroxide, NO, peroxynitrite and hypochlorous acid, respectively. Phagocytes also can convert nitrite to nitryl chloride and nitrogen dioxide via the myeloperoxidase enzyme or via hypochlorous acid. Ozone derived from singlet oxygen in inflammatory cells may also be a byproduct of oxidative stress that contributes to atherosclerosis. Other enzyme systems, including xanthine oxidoreductase and uncoupled NO synthase, may also contribute to increased oxidative stress in the setting of AKI.

Animal Models of Oxidative Stress in Acute Kidney Injury

Sepsis and Endotoxemia Sepsis is the most common etiology of AKI. Increased ROS production has been demonstrated to contribute to ischemic kidney injury in animal models, likely mediated through intense renal vasoconstriction. In the early phase of endotoxin-induced AKI, vasoconstriction may be mediated via activation of the sympathetic nerves and the renin-angiotensin system. The vasoconstriction can be counterbalanced through the vasodilatory effects of NO. However, progressed oxidative stress results in an increase in superoxide anion production, causing NO to be scavenged, thus leading to an imbalance favoring vasoconstriction and ischemic AKI. Wang and colleagues demonstrated that during endotoxemia-related AKI in mice, several antioxidants (including the superoxide dismutase mimetic Tempol) exert a protective effect by potentiating NO function.[38] Increased tissue levels of peroxynitrite, the product of the reaction between superoxide anion and NO, have also been detected in animal models of AKI.[39]

Ischemic Acute Kidney Injury The development of increased oxidative stress during acute renal ischemia-reperfusion has been reported in studies ranging over 2 decades. Furthermore, the concept that damaged endothelium contributes to the pathogenesis of acute kidney injury in models of renal ischemia goes back several decades to the pioneering work of Alexander Leaf and colleagues.[40] The injured endothelium may directly lead to oxidative and nitrosative stress through activation of endothelial NADPH oxidase and conversion of xanthine reductase to an oxidase. Increased oxidative stress may also result when injured or activated endothelium promotes infiltration of phagocytic cells into the injured kidney. Overexpression of the cell adhesion molecule ICAM-1 by vascular endothelium is upregulated in ischemic models of AKI, and blockade of ICAM-1 receptors attenuates injury.[41] A role for iron in mediating AKI through increased generation of oxygen free radicals has been demonstrated in a number of studies. In a rat model of ischemia-reperfusion injury induced by clamping the renal artery, pretreatment with the iron chelator deferoxamine prevented AKI development. In this study, urinary free iron concentration increased up to 20-fold during reperfusion.[42] Acute nitrosative stress also has been demonstrated to accompany increased oxidative stress in a rat model of acute kidney ischemia.[43] In this model system, administration of ebselen (a scavenger of peroxynitrite) prior to reperfusion was able to ameliorate ischemic kidney injury and to reduce lipid peroxidation and DNA damage in ischemic kidneys.

Nephrotoxic Acute Kidney Injury Increased oxidative stress also contributes to the pathogenesis of nephrotoxic AKI.[44,45] Walker and Shah demonstrated that increased oxidative stress also contributes to gentamicin-induced nephrotoxicity. While the precise mechanisms of gentamicin nephrotoxicity

remain unclear, gentamicin alters mitochondrial respiration and increases hydrogen peroxide generation. Gentamicin also has been demonstrated to induce superoxide anion and hydroxyl radical formation in renal cortical tissue.[46] Gentamicin may also mobilize iron from mitochondria, and rats treated with deferoxamine had significantly lower BUN levels and improved histology compared to untreated rats. Human studies have demonstrated excess iron accumulation in proximal tubule lysosomes in biopsies of patients with AKI.[47]

Injury from increased reactive oxygen species production also has been demonstrated in models of cisplatin- and cyclosporine A-induced nephrotoxicity. In the glycerol model of myohemoglobinuric kidney injury, the resulting rhabdomyolysis and hemolysis lead to the release and tubular cell absorption of heme proteins. Heme-loaded cells produce excess hydrogen peroxide, which can subsequently increase the release of iron from porphyrin compounds, thereby amplifying iron-dependent free radical generation. The resulting injury causes massive lipid peroxidation leading to cell death, a process that can be attenuated both in vitro and in vivo with the use of iron chelators such as deferoxamine.

Biomarkers of Oxidative Stress in Clinical Acute Kidney Injury

In vivo, oxygen intermediates are produced in minute quantities and have very short biological half-lives. The combination of low concentration and extreme reactivity make the in vivo detection of reactive oxygen species extremely difficult technically. In response to these difficulties, the most effective strategy for understanding the underlying in vivo mechanisms of oxidative injury is to detect stable products of redox chemistry reaction pathways. These so-called biomarkers of increased oxidative stress measure the oxidation of important macromolecules, including lipids, carbohydrates, proteins, amino acids, and DNA. The application of these biomarkers of increased oxidative stress to studies in the intensive care unit (ICU) setting have now unequivocally demonstrated that clinical AKI is an increased oxidative stress state, characterized, in particular, by alterations in reactive aldehyde and thiol chemistry.[48]

Pro- and Antioxidant Enzyme Gene Polymorphisms in Acute Kidney Injury

In clinical AKI, several gene polymorphisms have been described in key pro- and antioxidant enzymes that could potentially account for inter individual variability in the response to AKI. Perianayagam and colleagues recently examined gene polymorphisms associated with the NADPH oxidase enzyme and the antioxidant enzyme catalase (which metabolizes hydrogen peroxide) in a cohort of 200 patients with established AKI. A genotype-phenotype association was demonstrable between the NADPH oxidase genotype and plasma nitrotyrosine levels as a measure of increased oxidative and nitrosative stress. Furthermore, a genotype-phenotype association was also demonstrable between catalase genotypes and whole blood catalase activity. Of possible importance, the inheritance of an NADPH oxidase allele was associated with a 2.1-fold higher odds for dialysis requirement or hospital death.[49] These data suggest that propensity to increased oxidative stress may contribute to adverse outcomes in patients with established AKI. However, these results need to be confirmed in larger multiinstitutional studies.

NUTRITIONAL DERANGEMENTS IN ACUTE KIDNEY INJURY

AKI directly challenges the ability of the body's metabolism to augment recovery from illness. As AKI occurs most frequently in those whose capacity to efficiently process nutrients and meet basic tissue requirements is already compromised due to advanced age and chronic comorbidity, it is of little surprise that these patients are at high risk for prolonged hospitalization and death. A deeper understanding of how nutritional impairment in AKI may contribute to poor outcomes requires a discussion of its impact on the metabolism of three principle substrates.

Carbohydrate Metabolism

The Kidney and Glucose Metabolism

Glucose metabolism can be impaired by defects in insulin secretion from pancreatic ß-cells or from defects in cellular sensitivity to insulin. Each mechanism may result in hyperglycemia and diminished glucose tolerance (defined by elevated circulating glucose concentrations after an oral or intravenous glucose challenge). The kidney plays an important role in glucose metabolism. Studies using isotopic dilution techniques have demonstrated the renal cortex to be responsible for between 15% and 30% of total body gluconeogenesis, while the metabolically active medulla accounts for up to 20% of systemic glucose utilization.[50–52] As renal function declines, diminished clearance of insulin coupled with decreased glucose utilization due to loss of target organ function probably contribute to the insulin resistance observed in uremia.[53] Early animal studies have demonstrated that uremia is associated with both decreased hepatic and peripheral glucose uptake and insulin resistance indicated by a decrease in the amount of supplemental glucose required to prevent hypoglycemia during a fixed insulin infusion.[54,55] A more recent study reported that adipocytes from partially nephrectomized uremic rats also have a decreased number of glucose transporters.[56]

The extension of these findings to human studies was performed by DeFronzo and colleagues, who used insulin clamp techniques in chronic hemodialysis (CHD) patients to further characterize a diminished tissue sensitivity to insulin.[57] The site of this altered insulin sensitivity appears to be primarily a postreceptor defect of the phosphatidylinositol 3-kinase (PI3K)-Akt signaling, which is subject to influence from inflammation, oxidative stress, and the accumulation of "uremic toxins."[58,59]

Loss of Kidney Function Alters Insulin Dispersion

The kidney is a major site for the catabolism of plasma proteins with a molecular mass less than 50 kDa. Because most polypeptide hormones have molecular masses greater than

30 kDa, they are metabolized by the kidney to a variable extent. Renal metabolism of polypeptide hormones often involves the binding of the hormone after glomerular filtration to specific receptors in the basolateral membrane of tubular epithelia, which may be followed by uptake and either reabsorption or catabolism. The rate of glomerular filtration of peptide hormones is variable and dependent on molecular mass, shape, charge, and the degree of protein binding. For example, growth hormone, with a molecular mass of 21.5 kDa, has a filtration coefficient of 0.7, whereas insulin, with a molecular mass of 6 kDa, is freely filtered.

The kidney and liver are the major sites of insulin degradation. In humans, less than 1% of the filtered insulin is freely excreted in the urine. Instead catabolism of insulin in the kidney occurs after filtration-reabsorption and peritubular uptake. The kidney also catabolizes the insulin precursor proinsulin and C-peptide, with the kidney accounting for most of the catabolism of proinsulin. Renal extraction of each of these peptides is reported to be proportional to arterial concentration. In experimental studies, ligation of the renal pedicle results in a 75% increase in the levels of plasma insulin and a 300% increase in the levels of proinsulin and C-peptide. Conversely, the kidney accounts for only one third of the metabolic clearance rate of insulin, with liver and muscle accounting for the majority of the dispersion of this peptide. The kidney also accounts for about one third of the metabolic clearance of glucagon as a counter-regulatory hormone.

Growth Hormone and Insulin like Growth Factor I Axis

Growth hormone (GH, molecular mass, 21.5 kDa) has a somewhat restricted filtration rate of about 70%, compared to the rate for insulin. However, the kidney accounts for approximately 40% to 70% of the metabolic clearance rate of GH in experimental animal studies, and as a result, metabolic clearance is markedly decreased. In kidney failure, excess GH production also contributes to the high levels. Similar to insulin, less than 1% of filtered hormone is excreted unchanged in the urine. Many of the growth hormone biological effects are mediated by insulin like growth factors (IGF-I and IGF-II). GH stimulates the synthesis and release of IGFs, and circulating IGFs exert a negative effect on GH secretion, thereby forming a hormonal axis with negative feedback. Interestingly, the biological effects of IGF-I and IGF-II are blunted when assayed in the presence of uremic serum, suggesting that uremic factors interfere with biological activity.

Insulin Resistance in Critical Illness

Hyperglycemia, along with other aspects of insulin resistance, predicts death and morbidity in the critically ill and hallmarks the so-called *diabetes of injury*.[60–62] Recent observations suggest that up to 75% of ICU patients may have detectable insulin resistance on admission as assessed by homeostasis model assessment (HOMA) with about two thirds exhibiting overt hyperglycemia (serum glucose > 7 mmol/L or 126 mg/dl).[63] Traditionally, insulin resistance and hyperglycemia were considered to be a part of an overall adaptive response to increase substrate and energy availability during physiological stress.[61] However, it has become clear that these responses are unregulated, maladaptive, and may contribute to organ dysfunction, infection, polyneuropathy of critical illness, and mortality.[64–66]

Increased hepatic gluconeogenesis, glycogenolysis, and decreased insulin-driven peripheral utilization are the main effectors of this phenomenon.[60,67] Cellular uptake of glucose is predicated upon facilitated transport via the glucose transporter (GLUT) systems, a family of transport proteins distributed broadly among different cell types. The normal response to hyperglycemia is the downregulation of some of these transport systems, presumably to avoid intracellular glucose overload.[68] The GLUT-4 transporter is responsible for insulin-mediated glucose uptake in skeletal muscle, the main site of total body glucose disposal. The function of this transporter is often impaired in the setting of critical illness and hyperglycemia.[68,69] In contrast, the GLUT-1, GLUT-2, and GLUT-3 transporters operate *independently* of insulin and appear on multiple cell types including neurons, hepatocytes, endothelial cells, gastrointestinal mucosa, and renal glomerular and tubular cells.[68,70,71] Their upregulation during acute stress may partially account for the observed increase in total body glucose uptake, despite frank hyperglycemia and insulin resistance in critical illness.[72] Additional evidence suggests that intracellular accumulation of glucose has direct toxic effects on cellular function via enhanced generation of free radicals (oxidative stress) from increased uncoupling of oxidative phosphorylation.[73,74] Furthermore, this process also appears to have deleterious effects on mitochondrial ultrastructure and function within hepatocytes of critically ill patients not receiving intensive insulin therapy.[75]

The mechanisms by which insulin resistance ultimately leads to poor outcomes in critical illness are not fully established. As mitochondrial dysfunction and its resulting cellular energy depletion in critical illness have been implicated in the genesis of multiple organ failure, it may be that the observed benefit of intensive insulin therapy is due to a reduction in the amount of circulating glucose available for noninsulin-mediated GLUT transport and subsequent cellular glucose toxicity.[61] Indeed, one compelling finding from the two largest randomized controlled trials of intensive insulin therapy in the critically ill was a significant reduction in the occurrence of AKI patients receiving treatment.[76] It is also known that hyperglycemia hampers the immune system, largely through the impairment of neutrophil and macrophage function.[77] Insulin is also known to have an antiapoptotic role and antiinflammatory actions. Finally, as anabolic effects are known to extend beyond simple glucose metabolism, insulin resistance renders the body unable to effectively incorporate other nutrients.

Counterregulatory Hormones and Inflammation in the "Diabetes of Injury"

While the mechanisms remain to be completely elucidated, it is clear that excessive counterregulatory hormone and cytokine elaboration often couple to alter glucose metabolism. Elevation of several classic stress hormones including glucagon, epinephrine, norepinephrine, cortisol, and GH oppose the normal action of insulin.[78] Early infusion studies using these hormones resulted in marked elevation in hepatic glucose production in humans.[79,80] Epinephrine has been demonstrated to have multiple effects on glucose metabolism including impairment of insulin-mediated glucose uptake, increased glycogenolysis,

and enhanced gluconeogenesis.[81,82] Glucocorticoids are known to impair insulin-mediated uptake into skeletal muscle, likely via inhibition of GLUT-4 translocation to the plasma membrane.[83] Finally, GH exerts its effect through IGF-1, which has insulin like effects on cells. In excess, GH downregulates expression of the insulin receptor and appears to increase gluconeogenesis.[84]

As noted previously, severe illness often induces a generalized inflammatory response with the release of potent inflammatory mediators into the systemic circulation. Many of these mediators are known to be involved in both the pathogenesis of AKI and insulin resistance.[19,24,85,86] TNF-α, for example, has been associated with the development of insulin resistance in patients with renal impairment and those undergoing acute stress.[87,88] In addition to being secreted by macrophages, TNF-α also is found in skeletal muscle, where levels are known to inversely correlate with glucose disposal.[89] While the mechanism remains to be fully elucidated, a recent study demonstrated that infusion in humans directly suppresses phosphorylation of Akt substrate 160, leading to dysfunction of GLUT4 translocation and glucose uptake.[90] IL-6 is another proinflammatory cytokine with the potential to impact glucose metabolism and induce insulin resistance. It has been shown to inhibit insulin receptor tyrosine phosphorylation and downstream signaling in hepatocytes and in skeletal muscle in animal models.[91–93] Elevated levels of IL-6 also appear to predict insulin resistance in patients in times of acute stress such as cardiac surgery.[88]

Insulin Resistance in Acute Kidney Injury

The high prevalence of AKI in the acutely ill[2,94] and the known impairments of glucose metabolism resulting from loss of kidney function place AKI patients at extraordinarily high risk for insulin resistance. A large multicenter observational study of critically ill patients with established AKI recently demonstrated that hyperglycemia and insulin resistance are common and independently associated with poor outcomes.[95] In this study, insulin resistance, defined by hyperglycemia in the setting of hyperinsulinemia, was associated with increased mortality rates. Moreover, glucose levels over a period of 5 weeks were significantly higher in nonsurvivors compared to survivors, and insulin levels were higher in those who died, independent of demographics and severity of illness.

Whether or not hyperglycemia or hyperinsulinemia, or both, contribute directly to adverse events in patients with AKI, or simply reflect the severity of metabolic injury, has not been established. In addition to the potential glucotoxic mechanisms mentioned earlier, insulin resistance may itself influence outcomes through alterations in the IGF-1 and IGF binding protein (bp) axis, a critical component for insulin action. For example, increased levels of IGFbp 1, a major binding protein for IGF-1, suggest hepatic insulin resistance and appear to be higher in critically ill patients who die than who survive.[96] IGFbp 3, another binding protein for IGF-1, carries the majority (90%-95%) of circulating IGF-1 in a ternary complex consisting of IGF-1, IGFbp 3, and an acid-labile subunit. Timmins[97] detected that a protease directed against IGFbp3 is induced in critically ill patients diminishing availability of IGF-1 and IGFbp 3. In survivors, recovery is associated with decreased protease activity and subsequent levels of IGF-1 and IGFbp 3. These findings also are consistent with the aforementioned observational study of AKI where IGFbp 3 levels were lower and IGFbp 1 levels were higher in those who died.

In summary, insulin resistance is a serious metabolic consequence of AKI that has profound implications on glucose and energy homeostasis in a patient population with severe nutritional risk. Beyond its impact on carbohydrate metabolism, it also has implications for the use of other substrates including protein and lipids. Furthermore, insulin resistance rarely occurs in isolation, but often in concert with overt inflammation and oxidative stress to generate the deranged metabolic milieu in AKI and ultimately contribute to the poor outcomes observed.

Protein Metabolism

Perhaps the key metabolic challenge facing recovery from illness is the restoration of cellular scaffolding and machinery, functions critically dependent on the proper synthesis and assembly of proteins. The substrate for these tasks is amino acids derived from both the intake of exogenous sources and the catabolism of endogenous ones. The normal adaptive response to dietary protein restriction is to limit oxidative degradation of proteins and essential amino acids.[98] However, this preservation is altered in AKI and other acute illnesses, resulting in enhanced protein catabolism, principally reflected by excessive amino acid release from skeletal muscle and a negative nitrogen balance.[99–101] Daily protein catabolic rates in severe AKI have been reported to be 1.4 to 1.8 g/kg/day in several studies.[102–104] Additionally, there is a decrement in amino acid transport into skeletal muscle for protein synthesis, partly due to hepatic extraction to support gluconeogenesis and the synthesis of acute phase proteins.[105] The resulting imbalances in the use and clearance of both plasma and intracellular amino acid pools support this observed negative nitrogen balance and have been observed to be a sign of poor prognosis in patients with AKI.[106,107] Furthermore, recent evidence suggests that deranged protein catabolism may also directly impair endothelial function,[108] increase oxidative stress,[109] and weaken the immune response.[110]

Cellular homeostasis is predicated largely upon the coordinated breakdown of proteins by a highly regulated system known as the ubiquitin-proteasome pathway (UPP) system (Figure 47-4).[111] In muscle, for example, the enzyme caspase-3 first degrades myofibrillar proteins into component actin and myosin. These proteins are subsequently marked for degradation by covalent linkage to the protein factor ubiquitin by a series of conjugating enzymes. These reactions are repeated, forming a chain of several ubiquitin molecules sufficiently large enough to target the protein for degradation via a large proteolytic complex (the proteasome) into peptides and amino acids. The bulk of these amino acids are then recycled for use as an energy source or by the liver for gluconeogenesis. Several catabolic conditions including renal impairment (acute and chronic), sepsis, cancer, diabetes mellitus (DM), acquired immune deficiency syndrome (AIDS), and Cushing syndrome have been associated with increased activation of the UPP system. In AKI, contributions

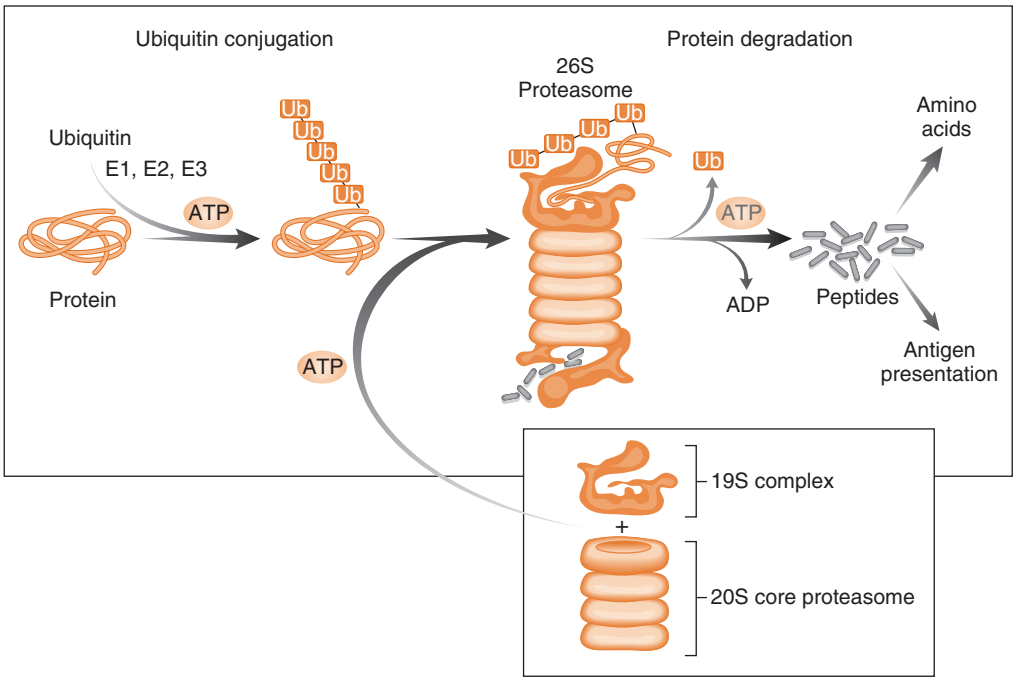


FIGURE 47-4 The ubiquitin-proteasome pathway (UPP) of proteolysis. Proteins degraded by the UPP are first conjugated to ubiquitin via activation of ubiquitin via the E1 enzyme in an ATP-dependent reaction. Activated ubiquitin is transferred to an E2 carrier protein and then to the substrate protein, a reaction catalyzed by an E3 enzyme. This process is repeated as multiple ubiquitin molecules are added to form a ubiquitin chain. In ATP-dependent reactions, ubiquitin-conjugated proteins are recognized and bound by the 19S complex, which releases the ubiquitin chain and catalyzes the entry of the protein into the 20S core proteasome. Degradation occurs in the 26S core proteasome, which contains multiple proteolytic sites within its two central rings. Peptides produced by the proteasome are released and rapidly degraded to amino acids by peptidases in the cytoplasm or transported to the endoplasmic reticulum and used in the presentation of class I antigens. *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate. (From W.E. Mitch, A.L. Goldberg, Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway, N. Engl. J. Med. 335 [25] [1996] 1897-1905. Copyright 1996 Massachusetts Medical Society. All rights reserved)

from hormone imbalances, metabolic acidosis, the dialysis procedure itself, and underlying inflammation have been shown to enhance UPP activity and underlie the observed imbalance between protein accretion and breakdown in this disease.[106,112]

Causes of Enhanced Protein Catabolism in Acute Kidney Injury

Renal Replacement Therapy

Renal replacement therapy engenders negative nitrogen balance through the loss of amino acids, and to a lesser degree, plasma proteins incurred during treatments. A standard intermittent hemodialysis (IHD) run with current high-flux dialysis membranes can result in as high as 8 g of amino acid loss into the dialysate.[113,114] Accompanying the potential for increased net solute and fluid removal with advent of continuous modalities, has been the equally greater capacity for further nutrient loss. Depending on the modality and pretreatment plasma protein concentrations, amino acid losses from continuous renal replacement therapy (CRRT) have generally been reported to be between 1.2 and 15 g/day, though as high as 20 to 30 g/day have been observed.[115–117] While heavily influenced by flow and filtration rates, convective clearance of amino acids may exceed that of dialysis by up to 30%.[118] This also has direct implications for nutritional support, because up to 17% of amino acids being received during the provision of TPN may be lost during treatment.[119] Furthermore, sophisticated studies in chronic hemodialysis patients have demonstrated markedly enhanced whole body and skeletal muscle protein catabolism during the treatment itself, probably through the induction of inflammation and oxidative stress.[120,121]

Metabolic Acidosis Metabolic acidosis is a common complication of advanced uremia and may represent another factor associated with increased protein degradation. Elegant studies in models of acute uremia have demonstrated that acidosis is associated with accelerated skeletal muscle proteolysis and is reversible with bicarbonate supplementation.[122,123] Subsequent mechanistic studies in chronic dialysis patients using tracer isotopes have revealed enhanced total body protein degradation that also was ameliorated upon correction of the acidosis.[124,125] How exactly acidosis contributes to protein catabolism is not entirely clear; however, concomitant glucocorticoid presence may play a permissive role evidenced by its requirement to stimulate degradation in other models of sepsis and acidosis.[122,126] Correction of acidosis with bicarbonate supplementation also has been demonstrated to improve insulin resistance. Mak and associates demonstrated that 2 weeks of oral bicarbonate replacement significantly improved insulin resistance in eight chronic hemodialysis patients as measured by hyperinsulinemic euglycemic clamp. The mechanism remains unclear but may be mediated through upregulation of vitamin D 1,25 $(OH)2D_3$ levels via enhanced renal 1-α hydroxylase activity.[127]

Insulin Resistance Often overshadowed by its effects on carbohydrate metabolism, insulin is the body's principle protein anabolic hormone with effects including the suppression of protein breakdown, and to a lesser extent, promotion of amino acid uptake. Early observations of insulinopenia in humans (i.e., uncontrolled Type I DM) illustrated a condition highlighted by negative nitrogen balance, hyperaminoacidemia, and profound lean tissue atrophy, findings now known to be reversible upon the provision of insulin. The underlying mechanism appears to be suppression of insulin receptor substrate-1-associated PI3K activity, resulting in stimulation of the UPP proteolytic system via caspase-3.[59] Investigations using tracer kinetic models and insulin clamp techniques have suggested that it remains the blunting of proteolysis rather than enhanced protein synthesis that belies the net protein anabolic effect of insulin in the postabsorptive state.[128,129] The lack of effect on protein synthesis is probably due to the insulin-mediated decrease in amino acid release into the blood stream. Biolo and coworkers examined protein metabolism in insulin-dependent DM patients and healthy subjects and found no differences in protein turnover in the fasting or fed state between the two groups.[130] However, several other studies indicated that muscle protein synthesis is sensitive to both insulin and concomitant increase in amino acid concentrations administered by intravenous infusion.[131]

Experimental studies suggest that enhanced protein catabolism not only applies to insulin-deficient states, but to insulin resistant ones as well. Studies in insulin resistant animal models have demonstrated increased protein degradation in skeletal muscle via enhanced activation of caspase-3 and the UPP system that was attenuated with the insulin-sensitizer rosiglitazone.[132] Chevalier and colleagues recently demonstrated a greater degree of whole-body protein breakdown and a suppressed protein anabolic response to insulin in relatively healthy obese women compared to their lean counterparts using a hyperinsulinemic, euglycemic, isoaminoacidemic clamp technique.[133] Dialysis patients with type II DM have been observed to have a marked increase in skeletal muscle protein breakdown compared to nondiabetic counterparts. As no significant difference in muscle protein synthesis was observed between the groups (at least in the fasting state), the net result was a significantly negative protein balance in the muscle compartment in the DM group.[134] This finding was later supported by prospective data identifying the presence of diabetes in dialysis patients as a potent independent predictor of loss of lean body mass over a 1 year follow-up interval compared to other variables including age, gender, albumin, incident malnutrition, inflammation, and modality.[135] The role of insulin resistance in this process was examined further in a group of chronic hemodialysis patients without diabetes or severe obesity.[136] Using stable tracer isotope methodology, a positive correlation was noted between the degree of insulin resistance as quantified by HOMA score and the amount of skeletal muscle protein breakdown. An interesting finding from this study was that while net balance trended towards being more negative in insulin resistance, HOMA score also correlated to a lesser degree with protein synthesis. This may reflect an imperfect adaptive mechanism to preserve protein stores in the face of increased substrate availability seen in diseases marked by enhanced catabolism such as AKI.

In summary, multiple lines of evidence suggest that insulin resistance is evident in AKI patients, is associated with enhanced protein breakdown, and represents a potential target for metabolic intervention.

Inflammation

Several lines of evidence implicate a role for inflammatory cytokines in the pathogenesis of enhanced protein catabolism in AKI. Experimental infusion studies with TNF-α have demonstrated an enhanced proteolytic effect on muscle protein and a reduction in protein synthesis.[137,138] Elevated IL-1 levels also appear in animal models to enhance muscle protein breakdown, which may improve with pharmacological blockade.[139] IL-6 has been demonstrated to be associated with accelerated muscle atrophyal, which may be through direct upregulation of the UPP system and attenuated by administration of IL-6 receptor antibody.[140,141] Further, in CHD patients, IL-6 has been demonstrated to be elaborated from skeletal muscle during hemodialysis, which correlates with protein catabolism, independent of amino acid availability.[121] Similarly, IL-6 and CRP levels have been shown to predict decline in serum albumin in stable hemodialysis patients despite protein intake.[142]

While the exact mechanism by which inflammation affects protein degradation in AKI is not entirely clear, one possibility involves its effects on insulin signaling. We have previously discussed how TNF-α infusion in healthy humans induced insulin resistance by suppression of glucose uptake and metabolism in muscle.[90] Inflammation may also contribute to the production of counterregulatory hormones, thereby affecting insulin signaling, which is a key modulator of the UPP system.[143]

In conclusion, protein metabolism is a dynamic process involving a delicate balance between ongoing synthesis and catabolism. Dysregulation of this process in AKI is described by an imbalance towards the latter, often overriding attempts at increasing synthesis. The net result is an ongoing negative nitrogen balance and loss of lean body mass with potential consequences for immune or organ function, liberation from mechanical ventilation, wound healing, and endothelial function. These effects, compounded with the diminished clearance of solutes and nitrogenous wastes in AKI, also have implications for the provision of nutritional support, which will be discussed later in this chapter.

Lipid Metabolism

Several studies suggest that lipid metabolism is profoundly altered in the setting of AKI.[144] In particular, the triglyceride content of lipoproteins is increased, while cholesterol content is decreased. This is true for low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The major cause of impairment in lipid metabolism appears to be due to inhibition of lipolytic enzyme function, including peripheral lipoprotein lipase and hepatic triglyceride lipase.[145] These abnormalities can be exacerbated if heparin is administered, including as an anticoagulant for dialysis therapy.[146] As a result of diminished lipolytic function, fat elimination is impaired. For example, if lipid is administered intravenously as part of parenteral nutrition, clearance of fat emulsion is

reduced by as much as 50%. This includes clearance of both long and medium chain triglycerides.[147] Although not well-studied, it also appears that plasma concentration many fat soluble vitamins (including vitamin A, vitamin D, and vitamin E) may be decreased in the setting of AKI. In contrast, vitamin K stores appear to be replete in this clinical setting.[148]

PROVISION OF NUTRITIONAL SUPPORT

While AKI patients have proven to be especially susceptible to PEW and its complications, several challenges confront the provision of nutritional support to this population. It is well-known, for example, that AKI patients are especially prone to fluid and solute overload from aggressive resuscitation, diminished clearance, and third spacing from underlying illness. Not only can this hinder accurate assessment of nutritional status, but can also heighten concerns over the potential consequences of overfeeding, including worsening azotemia, hyperglycemia, volume status, hypercapnia, electrolyte abnormalities, lipid toxicity, and increased infections.[149] These concerns, however, must be reconciled with observations that targeted goals of supplementation are often unmet in the ICU and are associated with adverse clinical outcomes.[150–153] Unfortunately, the provision of nutritional support in AKI remains hindered by a paucity of adequate randomized controlled trials targeting hard clinical outcomes. Additionally, the heterogeneity in type, timing, and severity of AKI and the varying comorbidity burden of these patients makes a uniform set of recommendations for all AKI patients unfeasible. Based on the available evidence, however, several recent reviews have been published.[154–157] Consensus guidelines based largely on expert opinion are also available for reference.[158–161] Of these, the European Society for Clinical Nutrition and Metabolism (ESPEN) has provided a specific examination of the data for AKI patients (Table 47-3).[158]

Assessment

Evaluating nutritional status can be difficult in AKI patients. Traditional anthropomorphic (BMI, body weight, triceps skin-fold) and biochemical measures (albumin, prealbumin, transferrin) are often confounded by volume status, which can easily obscure losses in lean body and fat mass in AKI patients. While several tools have been employed to characterize PEW and define metabolic requirements in AKI, none are without limitation. The SGA is a tool composed of historical elements of the patient's dietary habits, medical history, and physical exam.[11] It has been used in AKI patients to identify PEW and predict poor outcomes, but is not widely employed and can be difficult to administer in an ICU setting. Estimating equations including the Harris-Benedict and Schofield formulae have also been used to assess energy requirements but are also weight-based and originally validated in healthy individuals. They have been found to generally underestimate measured energy expenditure and require the addition of arbitrary "stress factor" multipliers.[162,163] BIA has been useful in assessing body composition in patients with CKD; however, it does not appear to predict acute changes in body water resulting from dialysis and has not been well-studied in AKI.[164] Indirect calorimetry, which measures oxygen consumption and carbon dioxide production, provides an assessment of energy expenditure. It is considered the gold standard in critically ill patients and is preferred over estimating equations, though widespread use may be limited by availability of a metabolic cart, expertise, and cost.[154,156,165,166] Measurements made by indirect calorimetry may also be affected by variations in ventilator and oxygen settings, patient agitation or thermogenesis, hypothermia (especially during CRRT), and loss of carbon dioxide via dialysis or ventilator/cuff leak.

TABLE 47-3 ESPEN Guidelines for Nutritional Requirements in Adult Patients with Acute Kidney Injury

NUTRITIONAL REQUIREMENTS IN PATIENTS WITH ACUTE RENAL FAILURE (NONPROTEIN CALORIES)	
Energy	20–30 kcal/kgBW/day*
Carbohydrates	3–5 (max. 7) g/kgBW/day
Fat	0.8–1.2 (max. 1.5) g/kgBW/day
Protein (essential and nonessential amino acids)	
Conservative therapy	0.6–0.8 (max. 1.0) g/kgBW/day
Extracorporeal therapy	1–1.5 g/kgBW/day
CCRT, in hypercatabolism	Up to maximum 1.7 g/kgBW/day

(Data from N. Cano, P. Fiaccadori, P. Tesinsky, et al., ESPEN Guidelines on Enteral Nutrition: adult renal failure, Clin. Nutr. 25 [2] [2006] 295-310, with permission from Elsevier.)
*Adapted to individual needs in case of underweight or obesity.

Energy Requirement

Observational studies using indirect calorimetry suggest that resting energy expenditure in AKI appears to be principally determined by the extent of the inciting event rather than by the renal impairment itself.[162,167] One study found an approximate 30% relative increase in resting energy expenditure in patients with sepsis-related AKI compared to healthy controls.[167] However, when patients with "isolated" AKI including such causes as drug-induced interstitial nephritis or glomerulonephritis were examined, there was no similar increase in energy expenditure relative to the same controls. Another study comparing indirect calorimetry versus estimating equations in stable mechanically ventilated patients could not demonstrate a marked increase in energy expenditure between those with and without kidney injury.[162] Based on these observations, ESPEN has recently recommended an energy intake of 20 to 30 kcal/kg/day (nonprotein calories) depending on estimated requirement. If estimating equations are to be used, it has been recommended that no more than 1.3 times the basal energy expenditure (BEE) used to estimate caloric requirement.[155,158]

Protein Requirement

As previously discussed, AKI and the need for renal replacement therapy (RRT) markedly enhance protein catabolism with normalized protein catabolic rates (nPCR) of between 1.4 and 1.8 g/kg/day.[102–104] Optimal dosing of protein in AKI and the appropriate target for nitrogen balance remain

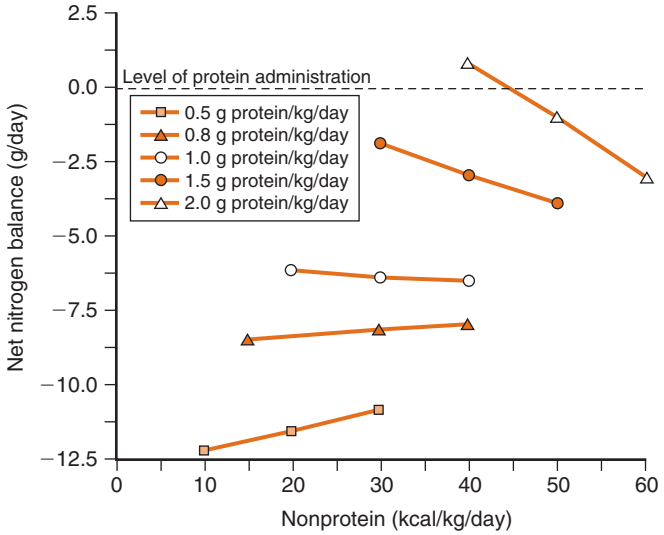


FIGURE 47-5 Interaction between net nitrogen balance and nonprotein calories at various protein intakes in patients with severe AKI receiving CVVH. Model assumes a patient weight of 68 kg and previous day's nPCR value of 1.59 g protein/kg/day. Net nitrogen balance was calculated using a predicted nPCR for a given level of energy and protein support. This figure illustrates that higher levels of protein may be necessary to achieve positive nitrogen balance in critically ill patients with AKI (Reprinted with permission from W.L. Macias, K.J. Alaka, M.H. Murphy, et al., Impact of the nutritional regimen on protein catabolism and nitrogen balance in patients with acute renal failure, JPEN J. Parenter. Enteral Nutr. 20 [1] [1996] 56–62.).

to be determined. An early observation of 40 patients on continuous veno venous hemofiltration (CVVH) estimated that between 1.5 and 1.8 g/kg/day of protein would be needed to achieve nitrogen balance.[168] Increases in the dose of protein supplementation were also accompanied by an increase in protein catabolism, though perhaps somewhat less with lower energy intakes of 25 to 35 kcal/kg/day (Figure 47-5). A subsequent nonrandomized study of AKI patients on CRRT compared a higher dose of dietary protein supplementation of 2.5 g/kg/day to a group of patients receiving standard of care 1.2 g/kg/day with both receiving equal amount of calories.[169] Patients receiving the higher dose of protein were more likely to achieve a positive nitrogen balance at any time during follow-up (53.6% vs. 36.7%; $P < 0.05$) and trended towards having less overall negative nitrogen balance but required more CRRT due to azotemia. Scheinkestel performed a study randomizing patients to either 2 g/kg/day or an escalating regimen of 1.5, 2, and 2.5 g/kg/day of protein supplementation with energy requirements estimated by Schofield equation or indirect calorimety.[107] Nitrogen balance was more likely to be positive with doses of greater than 2 g/kg/day associated with improved outcome after adjustment for age, sex, and severity of illness. A subsequent study examined the effect of varying energy intakes on achieving positive nitrogen balance using a crossover design in a small group of patients with acute renal failure (ARF)s.[170] Comparing 30 kcal/kg/day versus 40 kcal/kg/day using a fixed protein dose of approximating 1.5 g/kg/day, the higher energy regimen did not improve nitrogen balance and was associated with increased fluid administration, serum triglyceride and glucose levels, and insulin requirement. Based on the above data, ESPEN recommends protein dosing based on the expected degree of catabolism with 0.6 to 0.8 g/kg/day for conservative therapy, 1 to 1.5 g/kg/day for extracorporeal treatment, and a maximum of 1.7 g/kg/day in "hypercatabolism."[158] Clearly, further adequately powered, well-designed trials with clinical endpoints and safety monitoring are required to make more specific recommendations.

Lipids

Impaired lipolysis characterizes the main lipid abnormality of AKI resulting in hypertriglyceridemia, elevated very low-density lipoprotein (VLDL) and LDL levels, and diminished HDL levels. Consequently, it has been recommended that supplementation remain between 0.8 and 1.2 g/kg/day[170] with a general recommendations that total caloric intake from fat calories not exceed 25% to 35%.[155,171] This goal can usually be met with 10% to 30% lipid formulations. The benefits of medium-chain triglycerides in parenteral nutrition (PN) formulations compared to long-chain triglycerides remain unclear and are not widely available.[147] Frequent monitoring of triglyceride levels and liver function is also recommended, especially when PN is employed with adjustments made as necessary to avoid problems associated with hypertriglyceridemia.

Micronutrients

Alterations in the metabolism of vitamins and trace elements in AKI patients have not been well-studied. In patients receiving CRRT, losses of water-soluble vitamins in effluent have been reported, though few specific recommendations have been made for replacement. For example, while replacement of vitamin C has been recommended not to exceed 30 to 50 mg/day because of a reported risk of secondary oxalosis,[172] daily vitamin C loss in CRRT has been quantified between 68 and 100 mg/day.[173,174] Vitamin A is known to accumulate in renal impairment as a result of diminished clearance of retinol binding protein and retinol, which also are poorly dialyzed.[175] As a result, ESPEN recommends monitoring for signs and symptoms of vitamin A toxicity during supplementation, though variable levels have been observed.[148,175] Folate losses have also been reported in one study to be about 265 mcg/day.[173] Thiamine (vitamin B_1), vitamin B_6, selenium, zinc, and copper losses have also been reported in patients undergoing CRRT, with suggestions for replacement at doses greater than the recommended dietary allowance.[117,176]

Route

Enteral Versus Parenteral

Traditional teaching has suggested enteral nutrition (EN) as the preferred route of supplementation in the acutely ill, with purported benefits being maintenance of intestinal mucosa to minimize bacterial translocation, less infection risk, and lower cost.[177] While systemic reviews of the trials comparing PN versus EN have failed to demonstrate a clear mortality benefit with the latter, infectious complications do appear to be significantly reduced, possibly because of a

higher incidence of hyperglycemia and the need for central access with PN.[159,178,179] In support, a recent observational multicenter study of patients with severe sepsis or septic shock found the use of parenteral nutrition to be independently predictive of mortality (odds ratio [OR], 2.09; 95% CI, 1.29 to 3.37) despite similarities in mean glucose concentrations between those receiving PN versus EN.[180] ESPEN, the American Society for Parenteral and Enteral Nutrition (ASPEN), and the critical care group of Canada support the primary use of the EN route and do not recommend the routine exclusive use of PN in patients with functioning gastrointestinal tracts.[158,159,161] While few studies have addressed this question specifically in an AKI population, EN appears to be safe in patients with AKI, though a potential for elevated gastric volumes has been noted.[181] In such cases, there may be benefit for securing postpyloric feeding to ensure adequate caloric delivery and minimize possible pneumonia risk as long as it does not significantly delay therapy. Motility agents and semirecumbent positioning may also help to achieve these goals and minimize complications.[182,183]

For those who are unable to receive EN or meet their predicted energy requirements, PN may serve a useful adjunctive role in meeting metabolic demand, although it must be balanced against the attendant infection and hyperglycemic risks.[184] Limiting lipid replacement in the parenteral supplement may also reduce infection risk.[185] The optimal timing of parenteral supplementation is currently being studied in a large open-label randomized trial of critically ill patients in Europe (EPaNIC study).[186]

Type of Nutritional Therapy

Standard enteral formulae used broadly in critically ill patients are generally whole-protein solutions. While many are sufficient in protein content, they are often accompanied by a larger electrolyte burden. Other formulae containing peptides or amino acids in powder form are also available, although their use may be limited by nutrient variability, osmolality, and ease of administration. Several enteral formulas with mixed essential and nonessential amino acids have been adapted for use in chronic uremia (i.e., CHD patients) and have been recommended as a "reasonable" option for AKI patients, largely based on lower electrolyte content (potassium and phosphorous).[157,158]

The use of key additives to enteral nutrition designed to modulate inflammatory or immune response including glutamine, arginine, and omega-3 fatty acids have garnered interest in recent years.[187] The applicability of so-called *immunonutrition*, or more recently, *pharmaconutrition*, in critically ill patients has been examined in relatively small studies largely failing to demonstrate significant mortality benefit.[187] A recent relatively larger randomized clinical trial of 597 patients in critically ill adults did not demonstrate differences in clinical outcome.[188] Metaanalyses have also failed to suggest mortality benefit, although suggestion of a potential reduction in infectious complication rate exists.[189,190] In addition to being underpowered, heterogeneity in the patient populations and formulations applied may be contributing to the lack of a demonstrable effect.[187] Their benefit in specific patient populations remains to be studied, though a small trial in patients with sepsis demonstrated a relative improvement in severity of illness as measured by sequential organ failure assessment (SOFA).[191] Even less is known about their role in AKI; however, significant losses of glutamine (3.5–3.6 g/day) have been demonstrated in patients on CRRT, suggesting the need for supplementation, although dose and safety remain undetermined.[192] The lack of compelling evidence for immunomodulatory nutrition regimens has made them difficult to recommend for routine use in the critically ill or in AKI.[158,159,189]

METABOLIC SUPPORT

Intensive Insulin Therapy in Acute Kidney Injury

Given the discussed adverse impact that hyperglycemia and insulin resistance have on clinical outcome, attempts to control this derangement have been well-studied. Intensive insulin therapy designed to maintain blood glucose at or below 110 mg/dl was shown to reduce morbidity and mortality in a surgical ICU.[193] Although mortality data in a subsequent study from a medical ICU were equivocal, subgroup analysis suggested that benefit might be derived in those staying in the ICU for more than 3 days.[194] Additionally, predefined decreases in days of ventilator requirement and hospital/ICU length of stay were observed. A single-center, observational study of 531 patients admitted to the ICU found that control of hyperglycemia rather than increased insulin dosing to be responsible for improvements in mortality.[195] The effect of intensive insulin therapy in patients with established AKI remains to be determined; however, intensive insulin therapy has been postulated to have a role in the prevention of AKI.[76] Schetz and associates recently performed a secondary analysis of both Leuven trials and found that intensive insulin therapy was associated with reductions in the development of subsequent AKI using admission creatinine as a baseline value.[76] This effect was seen more prominently in surgical patients than medical patients, possibly because of lesser severity of illness in the former. The potential mechanism of benefit is unclear; however, it may be related to a decrease in cellular glucotoxicity or another metabolic effect of insulin such as reduction in protein catabolism or improvements in dyslipidemia. The answer, however, is not entirely clear-cut, because intensive insulin therapy carries with it significant hypoglycemic risk. This was illustrated in two subsequent trials in mixed ICU populations terminated early because of increased hypoglycemia in patients receiving intensive insulin therapy with neither showing improvement in short-term mortality.[196,197] Recently, results from a larger multinational prospective randomized trial (NICE-SUGAR Study) were published,[198] confirming these earlier signals regarding the potential harm of overly tight glucose control. This well-powered study involved 6104 critically ill patients anticipated to remain in the ICU for more than 3 days randomized to tight (81–108 mg/dl) or moderate (144–180 mg/dl) glycemic control using a uniform standardized intravenous insulin administration protocol. Using the primary endpoint of death at 90 days, intensive glucose control resulted in a higher rate of death (27.5% vs. 24.9%, $P = 0.02$) with severe hypoglycemia (blood glucose level ≤ 40) also observed more commonly

among patients undergoing intensive therapy (6.8% vs. 0.5%, $P < 0.001$). Of note, no differences in the need for or days of renal replacement therapy were observed between both groups despite similar renal function at study entry. Whether the differences in mortality were a direct result of hypoglycemia, increased administration of insulin, or some other effect on overall care administration remains unexplained.

The impact of the aforementioned studies on clinical practice remains to be seen; however, it is likely that attempts at modest glycemic control and the avoidance of the well-established complications of overt hyperglycemia will continue. As the attendant risk of hypoglycemia may be even more severe in patients with AKI, especially those requiring RRT,[194] attention to potential contributions from nephrological care to both hypoglycemia and hyperglycemia is warranted. For example, awareness of how changes in delivery or dose of RRT may impact glucose levels in patients receiving insulin therapy and the glucose content of dialysate or replacement fluids, or both, PN, and medications are paramount in reducing risk.[199]

Antioxidant Therapy in Acute Kidney Injury

The hypothesis that administration of appropriate antioxidants may be beneficial in patients with AKI is attractive given the relatively benign safety profile of most antioxidants, and the accumulating data on the role of oxidative stress in AKI. However, at the present time, there are no carefully controlled trials in the literature reporting the results of antioxidant administration in patients with AKI. In a small single-center observational study, Metnitz and colleagues[200] demonstrated that plasma levels of the antioxidants ascorbic acid, beta-carotene, and selenium are depleted in critically ill patients with multiorgan failure with and without AKI in comparison to healthy subjects. The investigators also demonstrated that plasma levels of these antioxidants were further depleted in patients to AKI in comparison to patients with preserved kidney function.

Several antioxidants have been evaluated in the ICU setting for treatment of increased oxidative stress associated with critical illness, albeit not specifically for AKI. N-acetyl-cysteine (NAC), a thiol-containing antioxidant, is known to be a safe agent with a relatively wide toxic to therapeutic window. Several small trials evaluating the use of NAC therapy for the treatment of acute lung injury in critically ill patients have been performed with mixed results. Similarly, PN enriched with the antiinflammatory fish oil eicosapentaenoic acid and antioxidants has been shown to reduce pulmonary inflammation and improve clinical outcomes in a small prospective randomized double-blind controlled trial in patients with ARDS. In a single-center randomized clinical trial, patients receiving methylene blue (an inhibitor of the NO pathway) had improved oxygen delivery, reduced body temperature, and reduced requirements for pressor support. In animal models of ischemic AKI, edaravone (a free radical scavenger) and mesna (a thiol-containing antioxidant) have demonstrated renoprotective effects and thus may be suitable for clinical trials in patients with AKI.

SUMMARY

In conclusion, AKI is a complex and devastating disease associated with a wide array of metabolic derangements resulting from loss of renal homeostatic function, the setting in which that loss develops, and the therapies it often engenders (i.e., RRT). The effects of these derangements including inflammation, oxidative stress, and insulin resistance can have profound implications for the use and catabolism of key substrates, use hindering the ability of afflicted patients to promote cellular recovery. While adequately designed and powered studies examining the optimal approach to metabolic and nutritional support in patients with AKI are lacking, it is clear that nutritional risk is high in this patient population and independently predicts morbidity and mortality. Consequently, frequent ascertainment of the nutritional and metabolic demands of patients is warranted, with an individualized therapeutic approach coupling the best-available evidence and guidelines for patients with comparable illness severity with vigilant monitoring for complications of overfeeding.

A full list of references are available at www.expertconsult.com.

Chapter 48

ACUTE KIDNEY INJURY: BIOMARKERS FROM BENCH TO BEDSIDE

Joseph V. Bonventre, M.D., Ph.D., and Venkata Sabbisetti, Ph.D.

ABSTRACT

The diagnosis of acute kidney injury (AKI) has relied on serum creatinine and urine output, two biomarkers that are insensitive and nonspecific especially early in the course of the syndrome. Additionally, creatinine and urine output are functional markers and not markers of injury. The lack of sensitive and specific injury biomarkers has greatly impeded the early diagnosis of AKI and limited the ability to predict outcome of the syndrome. Furthermore, the absence of early biomarkers has impaired the ability of investigators to design clinical trials to adequately evaluate the potential therapeutic efficacy of agents that might improve outcomes of AKI. A large number of biomarkers of kidney injury have been suggested and yet, for various reasons, none has been routinely accepted in animal or clinical studies. We review the rationale for biomarker development and the status of some of the more promising biomarkers, and provide reasons why the clinical use of these markers will transform the way that we diagnose AKI. Biomarkers of kidney injury also will enable the development of more efficient strategies to evaluate new therapeutic approaches to this common clinical condition, which continues to be associated with high morbidity and mortality.

BIOMARKERS IN ACUTE KIDNEY INJURY

AKI, previously referred as acute renal failure (ARF), represents a common clinical problem with high mortality. A multinational study of 29,269 critically ill patients admitted to the intensive care unit (ICU) revealed an overall occurrence of AKI requiring renal replacement therapy of 5.7% with an associated mortality of 60.3%.[1] The poor outcome associated with AKI has not improved in the past few decades despite progress in our understanding of the pathophysiology of AKI and advances in therapeutics and supportive care. AKI has been increasing in frequency[2] and continues to be associated with an unacceptably high in-hospital mortality of 40% to 80% in the intensive care setting.[3]

In current clinical settings, AKI is typically defined using either absolute or relative changes in serum creatinine (SCr) levels. The Acute Dialysis Quality Initiative (ADQI) developed a set of criteria for defining AKI, based upon serum creatinine levels and urine output, called the RIFLE (*R*isk, *I*njury, *F*ailure, *L*oss, and *E*nd-stage) criteria (Table 48-1). RIFLE uses relative changes in SCr and glomerular filtration rate (GFR) as criteria for its first three categories of risk, injury, and failure. Recently, in a further effort to standardize the definition of AKI, the ADQI and the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria (Table 48-2).[4,5,6] The AKIN group defined AKI as "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl ($\geq$ 25 μmol/L), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours)."

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes (a diagnostic biomarker), or pharmacological responses to a therapeutic intervention (a therapeutic biomarker).[7] Any parameter that can be measured, for example, proteins, lipids, genomic or proteomic patterns, imaging methods, electrical signals, and cells

TABLE 48-1 RIFLE Serum Creatinine and Glomerular Filtration Rate Criteria for Severity of Acute Kidney Injury

RIFLE STAGE	SERUM CREATININE AND GLOMERULAR FILTRATION RATE CRITERIA
R (risk)	> 150% of baseline serum creatinine, *or* > 25% dercrease in GFR
I (injury)	> 200% of baseline serum creatinine, *or* > 50% dercrease in GFR
F (failure)	> 300% of baseline serum creatinine, *or* serum creatinine of > 4 mg/dl (acute rise > 0.5 mg/dl) *or* > 75% dercrease in GFR

SCr increases are all relative to baseline values for individual patient.
Acute Dialysis Quality Initiative (ADQI) RIFLE criteria. *L* stands for "Loss," *E* for "End-stage."

TABLE 48-2 Acute Kidney Injury Network Serum Creatinine and Urine Output Criteria for Severity of Acute Kidney Injury

AKIN STAGE	SERUM CREATININE CRITERIA*	URINE OUTPUT CRITERIA
I	> 150% of baseline serum creatinine *or* ≥ 0.3 mg/dl increase in serum creatinine	< 0.5 ml/kg/hr for > 6 hr
II	> 200% of baseline serum creatinine	< 0.5 ml/kg/hr for > 12 hr
III	> 300% of baseline serum creatinine, *or* serum creatinine of > 4 mg/dl in the setting of an increase of ≥ 0.5 mg/dl	< 0.3 ml/kg/hr × 24 hr or anuria × 12 hr

*SCr increase are all relative to baseline values for individual patient.

present in urine, may serve as a biomarker. Biomarkers are of different types: disease biomarkers, toxicity biomarkers, mechanistic biomarkers, efficacy biomarkers, predictive biomarkers, and biomarkers of drug-target interaction. Some of these markers can serve as translational markers that can be used in both preclinical and clinical settings. A surrogate endpoint marker is a biomarker that can substitute for a clinical endpoint. A surrogate endpoint marker is expected to predict clinical benefit (harm or lack of benefit) based on epidemiological, therapeutic, pathophysiological, or other scientific evidence.[7,8] An ideal biomarker is easily measurable, reproducible, sensitive, cost-effective, easily interpretable, and would use readily available specimens (blood and urine). The widely accepted measure of biomarker sensitivity and specificity is the receiver operating characteristic (ROC) curve. An ROC curve is a graphical display of trade-offs between the true positive rate (sensitivity) and the false positive rate (1-specificity), when the biomarker is a continuous variable (Figure 48-1). A curve is generated and the closer the curve to the left-hand and top borders of the graph, the better the accuracy of the biomarker. The area underneath the ROC curve can range from 0.5 (useless test performing at the level of chance) to 1 (perfect test).[9] A perfect biomarker will have true positive rate of 1 and false positive rate of 0.

Creatinine as a Biomarker

Creatinine has been used as a biomarker of AKI for many years despite the widespread recognition of its shortcomings. First, creatinine production and its release into the

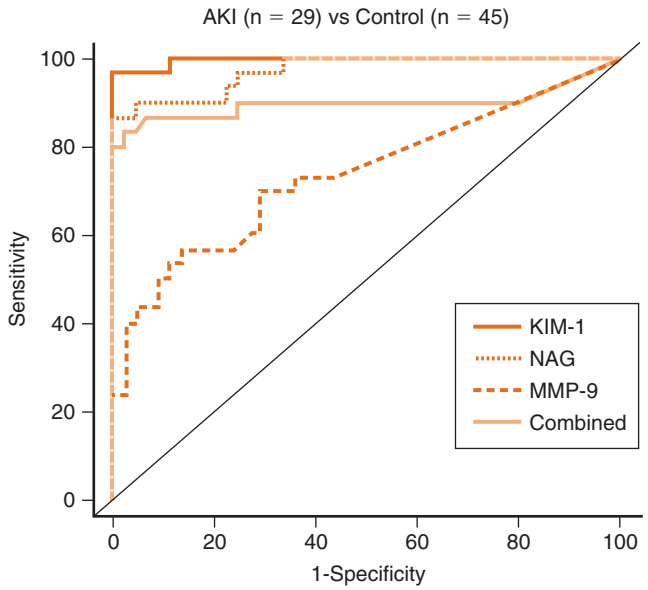


FIGURE 48-1 ROC analysis for normalized urinary biomarkers in a cross-sectional study. ROC curves of normalized MMP-9, NAG, and KIM-1 as a single test and in combination are plotted. The greater the displacement above and to the left of the line identified, the greater the likelihood that raised values of the test will identify AKI. (From W.K. Han, S.S. Waikar, A. Johnson, et al., Urinary biomarkers in the early diagnosis of acute kidney injury, Kidney Int. 73 [7] [2008] 863-869, with permission.)

circulation is highly variable with age, gender, meat intake, muscle mass, and diseases. For example, in certain disease states such as rhabdomyolysis, SCr levels may rise more rapidly, due to the release of preformed creatinine from the damaged muscle. Second, a static measure of creatinine does not depict the real-time changes in GFR resulting from acute changes in kidney function. Given the large amounts of functional renal reserve in a healthy individual and the variable amounts of renal reserve in patients with mild renal diseases, creatinine is not truly a sensitive marker, as it does not change until significant renal damage has occurred. When creatinine levels do increase, it often takes 24 to 48 hours after the AKI, and at this point in most cases, the acute event is remote in time and the likelihood that an intervention will alter the patient's course of kidney injury will be markedly diminished. Third, a drug-induced alteration in tubular secretion of creatinine might result in underestimation of renal function. Fourth, the creatinine assay is subject to interference because of intake of certain drugs or because of certain pathophysiological states including hyperbilirubinemia and diabetic ketoacidosis. Finally, SCr is nonspecific in conditions such as prerenal azotemia where creatinine levels can rise without tubular injury. Because of all these undesirable limitations of creatinine as a marker, there has been a great deal of interest in the identification of improved biomarkers for kidney injury. Furthermore, creatinine and blood urea nitrogen (BUN), biomarkers that have been used for decades for diagnosis and prognosis of AKI, are not direct metrics of tubular injury, but rather reflect functional changes. Urine microscopy is a time-honored test for evaluation of kidney injury, and seasoned physicians will attest to its value. Nevertheless, the sensitivity of this test as an early indicator of tubular injury in the kidney remains controversial.[10,11]

U.S. Food and Drug Administration Critical Path Initiative

Commenting on a major initiative of the U.S. Food and Drug Administration (FDA) that focuses on biomarkers, Janet Woodcock, M.D., Deputy Commissioner for Operations and head of FDA's Critical Path Initiative stated: "Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster."[12] The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product.[13] The FDA has provided guidelines that a biomarker can be considered "valid" only if the following conditions are met: 1) It is measured in an analytical test system with well-established performance characteristics; and 2) there is an established scientific framework or body of evidence that elucidates the physiological, pharmacological, toxicological, or clinical significance of the test result.

Need for New Biomarkers

There have been a number of advances in the application of biomarkers to AKI.[109] We are in need of new biomarkers of AKI for the following reasons: 1) Rather than being injury markers, the current blood and urine markers are functional consequences of the injury itself;[14] 2) creatinine, a central component of many of the definitions of AKI,[15] is a poor biomarker because of its aforementioned characteristics; and 3) we have an urgent need for novel biomarkers to diagnose AKI at early stages, to predict outcomes in a patient with AKI using standard therapy, identify who will respond to an intervention, and whether the intervention is actually working. Additionally, better biomarkers will permit better stratification of patients for clinical trials and potentially lead to identification of new therapeutics for AKI. The absence of sensitive and specific early biomarkers of AKI not only delays the diagnosis of AKI but also greatly impairs early intervention strategies and clinical trial design, thus delaying the initiation of potential therapies. A good predictive biomarker will have a significant effect on evaluation of potential therapies, as it will enable the identification of subgroups of patients who would be expected to have a high incidence of kidney injury. This will not only reduce the number of patients who are needed in the study for testing potential therapeutic strategies, but also aid in a better clinical trial design. It is likely that some of these biomarkers of AKI will also be useful for monitoring severity and progression of tubular interstitial disease in patients with chronic renal disease. In addition to their roles in early diagnosis, prediction, and patient outcome stratification, we also need biomarkers for the following reasons: 1) To determine the primary location of the injury in the kidney; 2) to differentiate AKI subtypes (prerenal, intrinsic renal, postrenal); 3) identify AKI associated with various etiologies; and 4) differentiate AKI from other acute kidney diseases.[16] The same biomarker may not satisfy all of these needs.

Blood and urine are two candidate fluids used to measure a particular biomarker of kidney injury. Urine has the advantage of being readily available noninvasively and amenable to straightforward testing by both healthcare professionals and patients themselves. Also, the low protein content of the urine in most clinical states makes urine more favorable for proteomic approaches. On the other hand, changes in urine flow rate will have effects on the concentration of an analyte, and variations in physical and chemical properties of urine may affect the stability of the analyte and reliability of the test. Serum samples are also readily available, and serum biomarkers may be more stable compared with urine. The presence of abundant proteins such as albumin and immunoglobulins in the blood leads to high interference and makes proteomic approaches more challenging.

Given the importance to the clinical, pharmaceutical, and regulatory communities of early intervention and better, safe therapies to improve patient care, there has been a great deal of activity in examining the role of various potential biomarkers of kidney injury in both animals and humans. Biomarkers have been proposed to reflect injury to various parts of the nephron or to reflect interstitial disease,[17] although in many cases, the specificity of particular biomarkers for specific nephron sites has not been sufficiently studied. The proximal tubule is the primary site of damage with ischemic injury or reperfusion injury, or both, and with most tubular toxins. Even if in some cases the primary site of injury is more distal along the nephron, the proximal tubule is often secondarily involved as well. While there are some important exceptions to this generalization, such as lithium toxicity that predominantly occurs at distal nephron, in general, a biomarker that is sensitive for proximal injury will be useful in many clinical scenarios and also very effective in safety monitoring and assessment.

An ideal AKI biomarker should have the following characteristics: 1) Be easily and reliably measured in a noninvasive or minimally invasive manner; 2) be stable; 3) be rapidly and reliably measurable at the bedside; 4) be inexpensive to measure; 5) be able to detect AKI early in the course; and 6) be predictive in its ability to forecast the course of AKI and potentially the future implications of AKI.

Specific Biomarkers of Acute Kidney Injury

There are many cellular proteins that are released into the urine and have been used in the past to monitor kidney injury in animals and humans.[18,19] In 1988, one of us (JVB) coauthored a review summarizing the status of noninvasive renal diagnostic studies.[20] The focus of that review was on β2-microglobulin (β2M), retinol binding protein, N-acetyl-glucosaminidase (NAG), adenosine deaminase binding protein, and L-alanine aminopeptidase. Some additional markers have received a good deal of attention since then, including α1-microglobulin (α1M), α-glutathione S-transferase (αGST), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), fatty acid binding protein (FABP), cystatin C (Cys-C), netrin-1, and osteopontin (OPN). Because of the limitations of the length of this review, we will focus

on an overview of important features of some of these markers without being able to do justice to the data available on each of the ones we discuss.

β2-Microglobulin

β2M is a low molecular weight protein (11.8 kDa) expressed on the cell surface of all nucleated cells. β2M is filtered and reabsorbed almost completely (~99%) and catabolized by the normal proximal tubule in humans. Megalin mediates the uptake of this protein in the proximal tubule. In healthy subjects, approximately 150 to 200 mg of β2M is synthesized daily. Any pathological state that affects the proximal tubule will result in an increase in β2M appearance in the urine. Elevated levels of β2M have been reported in several clinical settings, including cadmium toxicity,[21] cardiac surgery,[22] and renal allografts.[23] In idiopathic membranous nephropathy, β2M is identified as a superior independent predictor for the development of renal insufficiency.[24] Another study reported that β2M and Cys-C outperformed SCr for the detection of acute kidney injury in critically ill children.[25] The serum levels of β2M should be interpreted cautiously because the levels are altered significantly in various diseases, including rheumatoid disorders[26] and several types of cancers. A significant drawback associated with the use of urinary β2M as a marker of injury is its instability in the urine at room temperature particularly when the pH is less than 5.5. At body temperature, there is a rapid and irreversible loss of β2M, and at neutral pH it is digested by enzymes released by leukocytes in the urine.[27,28]

α1-Microglobulin

α1M is a glycoprotein of approximately 27 to 30 kDa primarily synthesized by liver, available both in free form and as a complex with immunoglobulin A. α1M is freely filtered at the glomerulus and completely reabsorbed and catabolized by the proximal tubule. Megalin mediates the uptake of this protein in the proximal tubule. Unlike β2M, α1M is more stable over a range of pH levels in the urine,[28] making it a more acceptable urinary biomarker. α1M quantitation in the urine has been reported as a sensitive biomarker for proximal tubule dysfunction in both adults and children.[29,30] In a small cohort of 73 patients, out of which 26 required renal replacement therapy, comparing α1M, β2M, cys-C, retinol binding protein, αGST, lactate dehydrogenase, and NAG early in the course of AKI, Herget-Rosenthal and colleagues found that urinary cystatin C and α1M have the highest ability to predict the need for renal replacement therapy.[31] Additionally, α1M also has been reported as a useful marker for proximal tubular damage and recovery in early infancy.[32] Limitations associated with α1M include the variation in serum levels with age; gender;[33] clinical conditions, including liver diseases,[30] ulcerative colitis,[34] human immunodeficiency virus (HIV), and mood disorders;[30] and the lack of international standardization.

N-Acetyl β-D Glucosaminidase

Urinary enzymes have been studied extensively as potential biomarkers of injury. With injury, enzymes normally present in the proximal tubular cells may be released into the lumen and, if stable, will appear in the urine. NAG is a 140-kDa proximal tubular brush border lysosomal enzyme, which is released into the urine after renal proximal tubule injury. There are two main NAG isoenzymes in human kidneys: isoenzyme A is the soluble part of the intralysosomal compartment and is normally secreted in urine by exocytosis, and isoenzyme B, a component of the lysosomal membrane is excreted in the urine during tubular injury. NAG levels are increased in the urine in a large number of toxin and nontoxin induced kidney injuries.[18,35] It is known, however, that some nephrotoxicants, in the setting of increasing kidney injury, can dose-dependently reduce urinary NAG activity by mechanisms not well-understood.[36] Furthermore, it has been shown that NAG levels are increased in a variety of conditions including, rheumatoid arthritis and hyperthyroidism where AKI is not present. Some of these reports, as is the case with many biomarker studies, may suffer from the comparison to a nonideal gold standard, because creatinine is often used, which, as described previously, is known to be unreliable as a sensitive marker of injury. Hofstra and associates[24] have reported that β2M is superior to NAG in predicting renal insufficiency in patients with idiopathic membranous nephropathy. NAG is inactivated at higher pH values in urine (about at pH 8).[37] In the same publication, the authors also reported that other urinary enzymes including alanine aminopeptidase, alkaline phosphatase, γ-glutamyltransferase, and lactate dehydrogenase are inactivated in urine at 37° C in low pH (about 5).

Interleukin-18

IL-18 is a proinflammatory cytokine, reported to play an important role in many human diseases, and is produced in a number of tissues. IL-18 is produced in the proximal tubule and is converted from its proform to the active form by caspase-1. IL-18 is a potent mediator of ischemic AKI in animal models and has been shown to contribute to tubular damage during ischemia-reperfusion injury.[38,39] In humans, IL-18 levels have been reported to be elevated in the urine of patients with AKI and delayed graft function compared to healthy individuals and patients with prerenal azotemia, urinary tract infection (UTI), chronic renal insufficiency, and nephritic syndrome.[40] In the same study, the urinary concentration cutoff for IL-18 at 500 pg/mg creatinine gave an optimal sensitivity (0.85) and selectivity (0.88) for the diagnosis of acute tubular necrosis (ATN). Parikh and colleagues have reported that IL-18 is an early, predictive biomarker of AKI after cardiopulmonary bypass (CPB), and that NGAL and IL-18 are increased in tandem after CPB.[41] Coca and colleagues, in an analysis of published literature, reported that the urine levels of IL-18 are significantly greater in patients with established ATN (area under the curve [AUC] =0.95) compared to all other types of patients including chronic kidney disease (CKD), UTI, and prerenal azotemia.[42] Furthermore, IL-18 has been shown to be a selective marker for predicting severity of AKI[41] and mortality in adult,[43] and critically ill children.[44] In four studies of urinary IL-18 as an early predictive biomarker of AKI in adults and children,[40–44] authors carried out ROC analysis of biomarker performance. In the four studies, AUCs for IL-18 varied from 0.54 to 0.9, suggesting IL-18 as a biomarker with variable sensitivity but with higher specificity for the early diagnosis of AKI.

Neutrophil Gelatinase-Associated Lipocalin

NGAL, also known as lipocalin-2 or Siderocalin, was first discovered as a 25-kDa protein in granules of human neutrophils. NGAL is normally expressed at low levels in a number of organs including kidney, breast, liver, small intestine, prostate, stomach, lymphoid cells, thymus, and lungs.[45] NGAL expression is upregulated in several cancers, including pancreas,[45] lung,[45] colon,[45] ovary, and breast.[46] Recently, high levels of NGAL have been reported in patients with brain tumors, and NGAL has been suggested as a biomarker for detection and monitoring of therapy.[47] NGAL is markedly elevated in many organs during inflammation[49,50] and ischemia.[51] Animal studies have shown NGAL to be promising as an early marker of ischemic and nephrotoxic kidney injury;[52] subsequently, a large number of studies have also evaluated the role of NGAL as a biomarker of AKI in humans.[53,54,55]

The early clinical studies with NGAL were done in children. Mishra and colleagues prospectively obtained serial urine and serum samples from 71 children undergoing cardiopulmonary bypass for surgical correction of congenital heart disease.[56] Of these 71 patients, 29% of eligible children were excluded due to preoperative use of ibuprofen, angiotensin-converting enzyme (ACE) inhibitors, gentamicin or vancomycin. Twenty children (28%) developed AKI, defined as a 50% increase in SCr. Both serum and urinary NGAL within 2 to 6 hours following CPB almost perfectly predicted which patients would subsequently develop AKI with an AUC of 0.91 and 0.99 for serum and urine respectively. A larger follow-up study of 120 children (using similar exclusion criteria) by Dent and coworkers showed that 2 hour postoperative serum NGAL was predictive of AKI (AUC-ROC 0.96) and correlated with postoperative change in serum creatinine, duration of AKI, and length of hospital stay.[57] A 12 hours, NGAL level strongly correlated with mortality. In a subsequent prospective study in children by Zappitelli and associates[58] where the AKI population was more heterogeneous with unknown timing of AKI, the AUCs of urinary NGAL for prediction of AKI were lower than the AUC reported in the Mishra and colleagues paper. The authors concluded that urinary NGAL is neither sensitive nor specific for predicting the course of AKI once it is established. Urinary NGAL levels were no different in survivors and nonsurvivors in any RIFLE[59] category. In this study, a number of patients had sepsis. Because NGAL can be produced by neutrophils and other organs besides the kidney, in clinical conditions such as sepsis or urinary tract infections, the appearance of this molecule in the urine might not directly reflect the severity of kidney injury.[60]

Wagener and colleagues reported that in adults, the best AUC for urinary NGAL concentration was 0.8 at 18 hours after surgery.[61] In another recent study by the same group in a cohort of 426 cardiac surgical patients, it was reported that NGAL has a limited diagnostic accuracy to predict AKI immediately after and 3, 18, and 24 hours, later cardiac surgery with an AUC of 0.573, 0.603, 0.611, and 0.584 respectively. Urinary NGAL, but not SCr levels correlated with cardiopulmonary bypass time and aortic cross-clamp time.[62] In a different adult population, however, urinary NGAL obtained on day 0 in recipients of kidneys from living or deceased donors performed well in predicting delayed graft function (AUC = 0.9).[44] In another study, NGAL levels were determined by western blot of urine samples from patients who entered the hospital via the emergency department. At a cutoff value of 130 mcg/g creatinine, sensitivity, and specificity of NGAL for detecting acute injury were 0.9 and 0.995, respectively. These values were better than those for NAG, α1-microglobulin, α1-acid glycoprotein, fractional excretion of sodium, and SCr,[63] although the AUC was equivalent for NGAL and SCr. Overall, NGAL represents a promising candidate as a biomarker for the early diagnosis of AKI.

Fatty Acid Binding Protein

Fatty acid binding proteins are expressed in several forms in many tissues. There are two primary forms of FABP in the kidney: the liver-type (L-FABP or FABP1) and the heart-type (H-FABP or FABP3). FABP1 is expressed in the proximal tubule, while FABP3 is expressed in distal tubule cells. FABP1 is absent in the kidney of rodents due to a silencing sequence in the upstream region of the promoter. Urinary levels of FABP1 are shown to be significantly upregulated in transgenic rodent FABP1 models of kidney injury, including ischemia or reperfusion, or both, cisplatin, folic acid, adenine, and cephaloridine.[64–68] The levels of FABP1 were markedly elevated as early as 2 hours after cisplatin administration, whereas a rise in SCr was not detectable until after 72 hours of cisplatin treatment.[68] Urinary FABP3 is increased with gentamicin toxicity in rodents.[67]

Much of the attention on urinary FABP has been directed at FABP1 in humans. Portilla and colleagues[69] reported that in humans, urinary L-FABP levels at 4 hours after surgery were an independent risk indicator for AKI (defined as a 50% increase in SCr over baseline) with an AUC of 0.81, sensitivity of 0.714, and specificity of 0.684 for a 24-fold increase in urinary L-FABP. Also increases in the urinary levels of both FABP1 and FABP3 predicted renal outcome in idiopathic membranous nephropathy patients with a calculated sensitivity and specificity of 81% and 83%, respectively for both of these markers.[70] In a recent study of 12 living kidney transplant related patients, immediately after reperfusion of their transplanted organs, a significant direct correlation was found between urinary L-FABP levels and both peritubular capillary blood flow and the ischemic time of the transplanted kidney.[71] The levels of urinary FABP1 should be interpreted with caution, however, as it may be influenced by a number of preexisting renal diseases, such as early diabetic nephropathy, nondiabetic chronic kidney disease, polycystic kidney disease, and idiopathic focal glomerulosclerosis.[16] Because FABP1 is expressed in other organs such as the liver, urinary FABP1 may lose specificity for kidney disease when there is coexisting liver disease. Nevertheless, in our preliminary studies, FABP1 performed well as a biomarker of AKI in adults with AKI. Multicenter studies with larger cohorts of patients will further define the predictive role of FABP1 as a biomarker for AKI and its sensitivity and specificity in patients with various etiologies of AKI.

Kidney Injury Molecule-1

KIM-1 is a type I cell membrane glycoprotein, which contains in its extracellular portion, a novel six-cysteine immunoglobulin like domain, two N-glycosylation sites, and a T/SP rich domain characteristic of mucin-like O-glycosylated proteins. In our lab, kidney injury molecule-1 (designated Kim-1

in rodents, KIM-1 in humans) was originally discovered in rodents using representational difference analysis (a PCR-based technique) after acute ischemic kidney injury, in an effort to identify molecules involved in the kidney injury.[72,73] Kim-1 mRNA levels in this screen were robustly upregulated in renal proximal tubular epithelial cells 24 to 48 hours after injury compared to other genes.

The ectodomain of KIM-1 sheds from cells both in vitro[74] and in vivo into the urine in rodents[75,76] and humans[77] after proximal tubular kidney injury. Elevated levels of soluble KIM-1 ectodomain in the urine were also demonstrated in patients with renal cell carcinoma.[78] This cleavage is mediated by metalloproteinases and regulated, at least in part, by mitogen-activated protein (MAP) kinase signaling pathways that are activated during stress.[79] Our recent studies demonstrated that KIM-1 acts as a scavenger receptor on renal epithelial cells, which converts the normal proximal tubule cell into a phagocyte, facilitates the clearance of dead cells in the lumen, and likely plays an important role in the innate immune response after injury.[80] This finding might offer new avenues to develop novel therapeutics to protect the kidney from acute injury, promote its repair, or both.

We have recently reviewed KIM-1, in the context of other biomarkers of kidney injury that are currently being evaluated.[18,19] In our studies, we demonstrated a strong correlation between tissue expression of KIM-1 and cleaved fragment of KIM-1 in urine. Characteristics of KIM-1 include much higher expression in the proximal tubular cell of the kidney than in any other cell of the kidney or any other organ, stability of the soluble ectodomain in the urine over a broad range of pH, sustained expression in proximal tubular epithelial cells until complete recovery, and undetectable levels in the healthy kidney, providing a high signal-to-noise ratio. These characteristics motivated our work and that of others in evaluating this molecule as a potential biomarker for kidney injury in both animal and clinical studies.

Kim-1 has proven to be highly sensitive and specific as a marker of kidney injury in many animal models, including but not limited to: ischemia,[73,76] donor brain death-induced injury, various toxins including cisplatin, S-(1,1,2,2-tetrafluoroethyl)-l-cysteine (TFEC), folic acid,[75] gentamicin, mercury, chromium,[81] cadmium,[82] iodinated contrast agents,[83] vancomycin, ochratoxin A, cyclosporine,[84] d-serine, and protein overload nephropathy.[85] Additionally, Kim-1 is highly efficient as a biomarker in aging-induced nephropathy[86] and angiotensin mediated injury in the Ren2 rats.[87] KIM-1 orthologues are present in many species besides rodents and man, including zebrafish, monkeys, and dogs. Kim-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker FDA and European Medicines Agency (EMA) qualification studies.[110]

In 2002,[77] we published our first study in humans linking urinary levels of KIM-1 to AKI. In this study, we demonstrated an increased expression of KIM-1 in kidney biopsy specimens from patients with a pathological diagnosis of ATN, with corresponding levels of KIM-1 ectodomain in the urine of these patients with clinically significant AKI. Notably, KIM-1 appeared in the urine prior to the appearance of casts. Since then, a number of studies have been published demonstrating the potential use of KIM-1 as a biomarker of AKI. In a cohort of 201 patients with clinically established AKI, Liangos and coworkers evaluated urinary KIM-1 and NAG in predicting adverse clinical outcome, and reported that elevated levels of urinary KIM-1 and NAG were significantly associated with the clinical composite endpoint of death or dialysis requirement, even after adjustment for disease severity or comorbidity.[88] KIM-1 is also a sensitive marker of kidney injury in children undergoing cardiac surgery.[89]

In patients with nondiabetic renal diseases, therapeutic interventions that reduce proteinuria including renin-angiotensin-aldosterone inhibition, sodium restriction, and/or diuretic therapies also reduced urinary KIM-1 levels, linking the degree of proteinuria to proximal tubule injury as quantitated by urinary KIM-1.[90] Van Timmeren and colleagues found that the amount of KIM-1 protein expression in proximal tubule cells correlated with tubulointerstitial fibrosis and inflammation in kidney tissue specimens from 102 patients, who underwent kidney biopsy for a variety of kidney diseases. In a subset of patients, whose urine was collected near the time of biopsy, urinary KIM-1 levels correlated with tissue expression of KIM-1.[91]

We quantified human KIM-1 protein expression in renal transplant biopsies by immunohistochemistry and correlated these findings with renal functional indices.[92] KIM-1 expression was detected in 100% of biopsies from patients with deterioration in kidney function and histological changes indicative of tubular damage. KIM-1 expression was significantly correlated with levels of SCr and BUN concentrations and inversely correlated with estimated GFR on the biopsy day. KIM-1 was expressed focally in affected tubules in 92% of kidney biopsies from patients with acute cellular rejection, reflecting the epithelial cell injury that comes as a component of severe cellular rejection. Focal positive KIM-1 expression was found in 28% of protocol biopsies in the presence of no detectable tubular injury on histological examination. This observation demonstrates the superior sensitivity of KIM-1 expression in detecting proximal tubule injury when compared to morphology alone. Van Timmeren and coworkers[93] also found that occurrence of renal allograft loss over time increased with increasing levels of KIM-1 excretion measured at baseline. High KIM-1 levels were associated with low creatinine clearance, proteinuria, and high donor age. KIM-1 levels predicted graft loss independent of creatinine clearance, proteinuria, and donor age.

We initially developed an enzyme-linked immunosorbent assay (ELISA) to measure Kim-1 in human and rodent samples and then developed a micro bead-based assay that is more sensitive with very good dynamic range, is rapid, requires less urine volume (30µl), and offers multiplexing capabilities.[76] Recently, our laboratory also developed a rapid diagnostic assay for measuring Kim-1/KIM-1 in urine samples by a dipstick method. This diagnostic assay can provide a sensitive and accurate detection of Kim-1/KIM-1, thereby facilitating the rapid detection of kidney injury in preclinical and clinical studies.[94]

In summary, Kim-1 is a very promising AKI biomarker. Its expression is not measurable in normal proximal tubule cells, but is markedly upregulated with injury or dedifferentiation. This protein is highly expressed on the apical membrane of the injured cells and its ectodomain is cleaved and excreted in the urine, reflecting kidney injury. Importantly,

Kim-1 excretion in the urine is highly specific for kidney injury since no other organs have been shown to express Kim-1 to a degree that would modulate its urinary concentrations. Urinary Kim-1 is much more sensitive than BUN and creatinine as a marker of injury in a large number of preclinical studies with a wide variety of kidney insults, including various toxins. Finally, KIM-1 is a translational biomarker, because its behavior in man mirrors its behavior in animals. Hence it is likely to be very useful in safety monitoring and drug development, particularly under conditions where there is toxicity noted in preclinical studies and a toxicity monitoring system must be put in place in order to advance the drug into clinical studies. Recently, the FDA and European Medicines Agency (EMEA) have included KIM-1 in the short list of kidney injury biomarkers that they will now consider in the evaluation of kidney damage as part of their respective drug review processes of animal studies of new drugs, and these regulatory agencies have encouraged its further use in clinical studies to amass more data on kidney biomarkers.[95]

Netrin-1

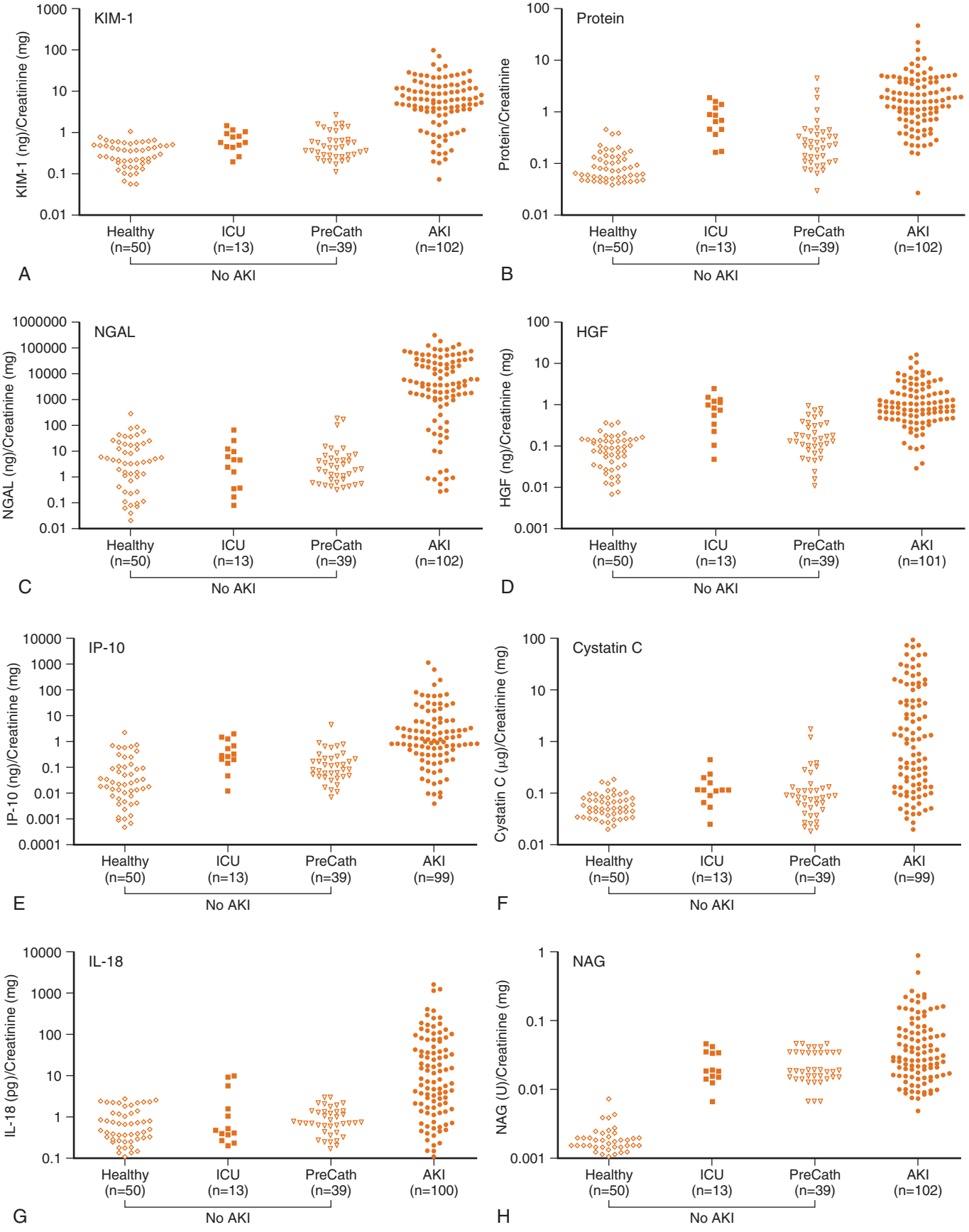
Netrin-1 is a 50–75 kDa, laminin like protein, initially recognized as a chemotropic factor that plays an essential role in guiding neurons and axons to their targets. Later studies revealed diverse roles of Netrin-1 in angiogenesis, adhesion, tissue morphogenesis, inflammation, and tumorigenesis processes. Wang and associates showed an upregulation of Netrin-1 in tubular epithelial cells in response to ischemia-reperfusion injury of the kidney in animal models.[96] In this study, Netrin-1 was excreted in the urine as early as 1 hour after kidney insult, increased more than 40-fold by 3 hours, and reached its peak levels (~50 fold) after the injury before the elevation of blood creatinine and BUN.[97] Further, the authors also tested the sensitivity and specificity of Netrin-1 in a toxin-induced kidney injury models in animals, using cisplatin, folic acid, and endotoxin (lipopolysaccharide). All of these kidney insults resulted in increases in the excretion of Netrin-1 in urine, supporting a potential role as an early biomarker for hypoxic and toxic renal injuries. Additionally, Reeves Ramesh and colleagues[97] also demonstrated a significant increase in urine levels of Netrin-1 in patients with established AKI from various etiologies (n=16) compared to healthy volunteers. Additional studies need to be done with larger cohorts for various AKI etiologies to further evaluate the importance of Netrin-1 as a potential biomarker of AKI.

Osteopontin

OPN is a multifunctional 44 kDa phosphoprotein, widely distributed in a variety of tissue types ranging from bone to epithelial cells of the gastrointestinal (GI) tract, lungs, breast, salivary glands, inner ear, placenta, and kidneys.[98,99] OPN has been associated with a variety of physiological and pathological functions, including bone modeling, immunity, cell adhesion, and migration. OPN is expressed in ureteric buds and few interstitial cells of fetal kidney, whereas in the normal adult kidney, OPN is localized primarily to the distal tubule and thick ascending segments of the loop of Henle.[100] During renal disease, however, OPN has been shown to be upregulated in all tubular segments, including proximal tubules.[100] In normal healthy individuals, daily OPN excretion is 3805 ± 1805 mcg/24 hours or 21.4 ± 6.2 mg/g of creatinine.[101,102] OPN is secreted in the urine and inhibits the formation of calcium oxalate kidney stones. OPN has been evaluated in various experimental models of kidney injury, and multiple studies have reported the detection of OPN mRNA in regenerating proximal tubules in renal ischemia models.[103,104] The elevated levels of OPN are sustained for 7 days after the injury. In gentamicin-induced acute tubular necrosis in rodents, OPN is detected only in the cortical distal tubules during first few days of the injury, but is markedly elevated in regenerative proximal tubules after day 15.[105] Additional studies are required in humans to evaluate the utility of osteopontin as a urinary kidney injury biomarker.

Comparison of Multiple Urinary Biomarkers

In a cross-sectional study, we evaluated the diagnostic performance of nine urinary biomarkers of AKI: KIM-1, NGAL, IL-18, hepatocyte growth factor (HGF), Cys-C, NAG, vascular endothelial growth factor (VEGF), chemokine interferon-inducible protein 10 (IP-10; CXCL10), and total protein in 102 patients with AKI of various etiologies and 102 individuals without clinically documented AKI (Figure 48-2).[106] The control group included healthy volunteers, patients scheduled for cardiac catheterization, and patients who were in the ICU but not diagnosed with AKI. For each of the urinary proteins, median concentrations were significantly higher in patients with AKI than those without AKI. The area under the AUC-ROC for KIM-1 was 0.95, when the AKI patients were compared to healthy control patients. When we took a nonbiased logistic regression model approach to optimize the combination of biomarkers, so as to yield an algorithm that could best fit the data and be prospectively tested, we obtained the following: (risk score of $2.93 \times [\text{NGAL}>5.72 \text{ and } \text{HGF}>0.17] + 2.93 \times [\text{PROTEIN}>0.22] - 2 \times [\text{KIM}<0.58]$). This combination of four biomarkers yielded an AUC (0.94) that was significantly greater than individual biomarker AUC-ROCs when a number of hospitalized control groups were included (even though some of these "controls" likely had clinically silent AKI). It is particularly interesting to examine the scatter plots of urinary biomarkers across the four groups (see Figure 48-2). From Figure 48-2, it is clear that there was little overlap between the AKI group and the healthy controls for KIM-1, total protein, NGAL, NAG, and HGF. The overlap may be due to misdiagnosis, either due to an incorrect diagnosis of AKI clinically, or because creatinine can be elevated in the absence of kidney injury in patients with prerenal azotemia. Alternatively in this cross-sectional analysis, a few patients may be already in a postinjury or tissue repair state with lower biomarker levels, despite the fact that serum creatinine had not yet fallen completely back to normal. NAG was the best performer when comparing AKI patients to healthy volunteers, but its performance deteriorated when the other control groups were included, especially the ICU group with no clinical or laboratory diagnosis of AKI. In the latter group, NAG was elevated in 13 of 13 patients. Age-adjusted levels of urinary KIM-1, NAG, HGF, VEGF, and total protein were significantly


KIM-1
KIM-1 (ng)/Creatinine (mg)
1000
100
10
1
0.1
0.01
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=102)
No AKI
A
Protein
Protein/Creatinine
100
10
1
0.1
0.01
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=102)
No AKI
B
NGAL
NGAL (ng)/Creatinine (mg)
1000000
100000
10000
1000
100
10
1
0.1
0.01
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=102)
No AKI
C
HGF
HGF (ng)/Creatinine (mg)
100
10
1
0.1
0.01
0.001
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=101)
No AKI
D
IP-10
IP-10 (ng)/Creatinine (mg)
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=99)
No AKI
E
Cystatin C
Cystatin C (μg)/Creatinine (mg)
100
10
1
0.1
0.01
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=99)
No AKI
F
IL-18
IL-18 (pg)/Creatinine (mg)
10000
1000
100
10
1
0.1
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=100)
No AKI
G
NAG
NAG (U)/Creatinine (mg)
1
0.1
0.01
0.001
Healthy (n=50)
ICU (n=13)
PreCath (n=39)
AKI (n=102)
No AKI
H

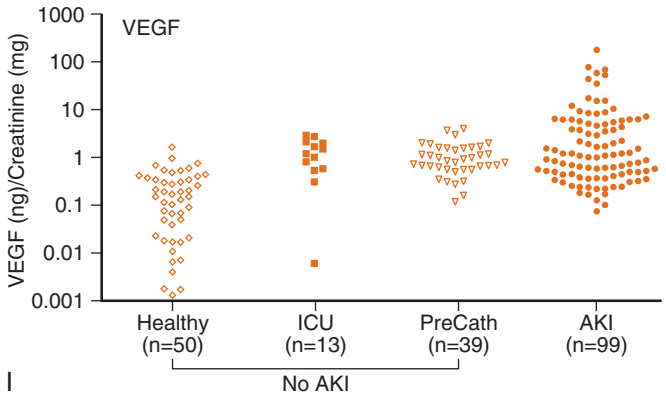


FIGURE 48-2 Urinary biomarker levels (A, Kim-1; B, Total protein; C, NGAL; D, HGF; E, IP-10; F, Cystatin C; G, IL-18; H, NAG; I, VEGF.) in patients with a diagnosis of AKI as compared to three control groups without this diagnosis. Patients with documented AKI of at least the "Risk" category of the RIFLE criterion[108] (peak SCr > 50% increase over admission value or known baseline) were recruited from the inpatient nephrology consultation service of the Brigham and Women's Hospital. Causes of AKI were obtained by detailed chart review including the treating nephrologist's consultation note and evaluation of laboratory data by a coauthor not involved in the patients' care. Individuals without AKI were selected from three distinct populations: healthy volunteers, patients undergoing cardiac catheterization, and patients admitted to the intensive care unit. Healthy volunteers were excluded if they reported a recent hospitalization, diagnosis of chronic kidney disease, or treatment with nephrotoxic medications (nonsteroidal antiinflammatory drugs were allowed). Patients undergoing cardiac catheterization and those admitted to the intensive care unit were included in the non-AKI cohort if they had normal urine output (> 0.5 ml/kg/hr), stable SCr during hospitalization (< 0.3 mg/dl change from baseline), and an estimated GFR > 50 ml/min. Urine samples from cardiac catheterization patients were taken before administration of intravenous contrast.

Urine was collected from spontaneous voids or from indwelling Foley catheters. The urine supernatant was aliquoted into 1.8 ml Eppendorf tubes and frozen within 2 hours of collection at −80° C. At the time of assay, samples were thawed, vigorously mixed and centrifuged at 14,000 rpm at 4° C and 30 to 100 µl of supernatant was taken by pipette for biomarker measurement. Assays for KIM-1, total protein, NGAL, HGF, IP-10, cystatin C, IL-18, NAG, and VEGF were performed within 3 months of urine collection after a maximum of three freeze-thaw cycles. Urine samples from patients with established AKI were collected close to the time of initial consultation. Each point represents one subject. (From V.S. Vaidya, S.S. Waikar, M.A. Ferguson, et al., Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans, Clin. Trans. Sci. 1 [3] [2008] 200-208, with permission).

higher in patients who died or required renal replacement therapy (RRT), when compared to those who survived and did not require RRT.[106]

THE FUTURE OF BIOMARKERS IN ACUTE KIDNEY INJURY

A significant amount of progress has been made over the last few years in the discovery, characterization, and validation of new biomarkers, which will ultimately improve the care of patients. Additional work, however, still needs to be done in bringing these biomarkers successfully to clinical practice for AKI. Studying these biomarkers in animals, one has the luxury of a true gold standard of toxicity-histological analysis of the kidney. In humans, we are often left to evaluate biomarkers using very poor metrics. For example, we rely on serum creatinine for the definition of AKI, and yet we know that this marker is very insensitive and nonspecific for kidney injury. Therefore, prospective studies in humans using modest changes in serum creatinine to determine AKI are going to be subject to ambiguity in interpretation. We know in rats, for example, that the sensitivity of creatinine for mild tubular toxicity is low, while other markers are much more sensitive (unpublished data). We also have to be very clear about the context in which we intend to use the biomarker. Are we interested in a biomarker that tells us that there is injury? What if a study shows that this biomarker does not predict outcome? That does not mean it is a bad biomarker. The link between injury and outcome is quite convoluted and certainly very poorly understood.

As AKI is a complex disease with multiple etiologies and often occurs in the setting of systemic diseases, one biomarker may not suffice for early diagnosis and prediction of clinical course. We may benefit from multiple biomarkers (plasma and urine) that can provide early evidence of risk, injury, and have the ability to distinguish between different types of AKI in both adults and pediatric patients. In a recent study of patients undergoing cardiac surgery, Han and associates reported that prediction of AKI at 3 hours after surgery using KIM-1, NAG, and NGAL significantly improved with use of a combination of biomarkers, compared to the performance of individual biomarkers.[107] Furthermore, development and application of standardized mathematical algorithms is extremely important to interpret the data from biomarkers in a panel to predict the risk, severity, and trajectory of AKI.

In summary, we have come far but we have to go much further. We should not fall into the trap of waiting longer for the "messiah" biomarker. We have many very good "prophets" that would be clinically applicable. It will take time to validate them in all the conditions, but we should proceed with haste with what we have, while simultaneously sending out scouts for others.

ACKNOWLEDGMENTS

Work described from Dr. Bonventre's laboratory was supported NIH grants DK39773 and DK72831.

DISCLOSURES

Dr. Bonventre is coinventor on patents for KIM-1, which have been licensed to Biogen-Idec, Genzyme Corp., and Johnson and Johnson. He has received consulting fees from Genzyme and Johnson and Johnson and a grant from Johnson and Johnson.

A full list of references are available at www.expertconsult.com.

Chapter 49

PHARMACOLOGICAL INTERVENTIONS IN ACUTE KIDNEY INJURY

Mark Douglas Okusa, M.D., and Rasheed Abiodun Balogun, M.D.

Pharmacological therapy of acute kidney injury (AKI) has been largely unsuccessful despite proven benefits seen in preclinical studies. Prevention and treatment of AKI is indeed an important clinical issue as mortality in patients with AKI, especially in critically ill patients, remains alarmingly high despite substantial advances in techniques of resuscitation and renal replacement therapy. Based upon databases of U.S. hospitalizations over the past 10 to 15 years, the incidence of AKI is increasing markedly[1,2] as a result of the expansion of invasive medical and surgical procedures and the increasing expectation for aggressive medical management of critically ill patients. In critically ill patients, mortality is 40% to 60%[3–6] and traditionally has been attributed to comorbid conditions. Accumulating data suggests, however, that AKI has an independent negative impact on mortality.[7,8] Chertow recently reported that even a rise of serum creatinine of 0.3 to 0.4 mg/dl was associated with an increase in mortality (multivariable odds ratio [OR], 1.7; 95% confidence interval [CI], 1.2 to 2.6).[9] Recently, two classification schemes have been described, the Acute Dialysis Quality Initiative (ADQI) classification, called RIFLE (*R*isk, *I*njury, *F*ailure, *L*oss and *E*nd-stage), and Acute Kidney Injury Network (AKIN) staging (I, II, III) based upon graded levels of rise in serum creatinine or decrease in urine output.[4,10] Even the least severe category, "R" or AKIN stage I, was associated with a mortality rate of 30.9% or 30.7%, respectively.[11] These studies highlight the important effects of a small decline in GFR on the overall outcome of critically ill patients.

Although many animal studies have demonstrated that different classes of pharmacological agents are effective in preclinical studies, few have been shown to be beneficial in human studies of AKI. For these reasons and because of the high morbidity and mortality associated with AKI, a better understanding of the barriers to the prevention and treatment of AKI is necessary. Significant efforts are currently being directed in an international and multidisciplinary manner to improve outcomes in such patients by finding ways to prevent AKI, establishing early diagnoses and treatments with both nonpharmacological and pharmacological interventions.[12–14] With a refined and consistent definition of AKI and point-of-care use of novel biomarkers for the early identification of AKI,[12,15,16] new and old pharmacological therapies will require testing (or retesting) in randomized clinical trials.

This chapter will focus on pharmacological agents that have been used to prevent or treat AKI clinically with variable levels of proven success (or failures) and also those with promising data from recent experimental studies of AKI in animals and humans.

BARRIERS TO SUCCESSFUL CLINICAL TRIALS IN ACUTE KIDNEY INJURY

Patient and Comorbid Factors

The changing spectrum of human illnesses is an important variable to consider in the outcomes of interventional studies. Recent studies of AKI have noted a trend of increasing severity of comorbid and extra renal complications.[1,2,17] Those patients with higher comorbidity were associated with a higher incidence of AKI, especially if they were on mechanical ventilation.[2] In a multicenter study of 618 patients with AKI in the intensive care unit (the Program to Improve Care in Acute Renal Disease Network [PICARD]), the incidence of comorbid conditions was high including, 30% with chronic kidney disease (CKD), 37% with coronary artery disease, 29% with diabetes mellitus (DM), and 21% with chronic liver disease. AKI was accompanied by extra renal organ system failure in most patients. These comorbid conditions are likely contributors to failed treatment regimens.

Preexisting renal disease is the most important factor in predicting AKI following exposure to radiocontrast agents, major surgery, and other medical conditions.[18] In a recent study, 1764 patients who developed hospital-acquired AKI and were treated with dialysis were compared to more than 600,000 patients who were hospitalized but did not develop AKI requiring dialysis.[19] In the group of patients with AKI requiring dialysis, 74% occurred among patients with an estimated glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2. The more severe the baseline CKD, the greater the risk of AKI: two fold increase among patients with estimated GFR (eGFR) 45 to 59 ml/min/1.73 m^2 and 40-fold increase among patients with eGFR <15 ml/min/1.73 m^2. These results and results from other studies strongly suggest that underlying CKD maybe the single most important risk factor for AKI.

Pathogenesis of Acute Kidney Injury is Complex

The pathogenesis of AKI is complex; whereas initiating events may be dissimilar (ischemia or toxins are major factors that precipitate injury), subsequent injury responses may involve similar pathways. The complexity of AKI is illustrated in the following example. AKI associated with ischemia due to a reduction of renal blood flow (RBF) below the limits of blood flow autoregulation leads to maladaptive molecular responses. These responses lead to endothelial and epithelial cell injury following the onset of reperfusion.[20] Pathogenic factors such as vasoconstriction, leukostasis, vascular congestion, apoptosis, and abnormalities in immune modulators and growth factors have formed the basis of rational therapeutic interventions.[21–25] However, many of these targeted therapies have failed, are inconclusive, or have yet to be performed.[26,27] Given the complexity of the pathogenesis of AKI, it may be naïve to expect that one therapeutic intervention would have success unless that intervention focuses on prevention of AKI and targets a specific initiating etiology. Given the multiple overlapping pathways involved in AKI, therapies may need to simultaneously target multiple pathways to achieve success.[28]

Acute Kidney Injury is a Multisystem Disease

If in fact small changes in serum creatinine are independent predictors of increased mortality, why then do these patients with AKI die? In intensive care units (ICUs) it is not uncommon to observe complicated medical conditions that arise from the dysfunction of one organ leading to the dysfunction of another. In a cohort of patients with AKI following radiocontrast, many developed complications after the onset of AKI including sepsis, hemorrhage, central nervous system manifestation, and respiratory failure.[8] Thus AKI in some cases is thought to lead to distant organ dysfunction syndrome leading to fatality in such patients. Experimental studies provide some insight as to the mechanism by which isolated events leading to the loss of GFR can lead to distant organ dysfunction. Many potential factors may lead to distant organ effects including circulating factors such as cytokines and chemokines, activated leukocytes, and adhesion molecules leading to immune cell infiltration. Oxidative injury, apoptosis, and cellular necrosis contribute to the final pathway of organ dysfunction. In critically ill patients, coexistent AKI and acute lung injury is associated with high mortality of 58% to 80%.[29,30] Experimental studies demonstrated increased pulmonary vascular permeability, lung edema, alveolar hemorrhage, and leukocyte circulation following ischemic AKI.[31–33] These data are scientifically and clinically relevant in defining the complex cross talk between the lung and kidney and will provide insight into human AKI. Klein and colleagues[34] show that interleukin-6 (IL-6) is a direct mediator of AKI-induced increase in vascular permeability, leukocyte circulation, and increased edema following bilateral ischemia-reperfusion injury (IRI) or nephrectomies.[34]

Liu and associates[35] showed that mice with AKI exhibited increased brain vascular permeability and an increase in the level of glial fibrillary acidic protein, a marker for activated glial cells during brain inflammation and activated microglial cells (brain macrophages) that were associated with increased numbers of pyknotic neurons. Thus central nervous system (CNS) manifestations of AKI may be the result of distant effects of AKI induced inflammation.

AKI promotes cardiac injury that is characterized by hypertrophy and fibrosis.[36] AKI has been shown to increase cardiac apoptosis and production of IL-1 and tumor necrosis factor (TNF),[31] cardiac hypertrophy and fibrosis,[36] and gene expression for the macrophage chemokine osteopontin. These effects lead to an increase in inflammation[37] and abnormal cardiac function.[31]

In conclusion, while AKI is an independent risk factor for mortality,[7] in most studies of AKI, renal failure per se is usually not the cause of death.[28] The potential systemic effects of AKI involve multiple organs and lead to high mortality. Thus the complexity created by the systemic effects of isolated AKI may have contributed to ineffective treatments in past clinical trials. These observations also suggest that potential therapeutic strategies should not be limited to treatment of kidney injury alone but should be broadly based to treat systemic effects of AKI.

PHARMACOLOGICAL INTERVENTIONS

Pharmacological interventions can be expected to be useful when used at various points in the natural history of AKI. Theoretically, these would include agents that are used to lower the risk (i.e., prevent) in patients identified with high risk of AKI, agents that are used to limit injury in established AKI, and those that improve outcomes by improving rates of recovery from AKI. Currently more clinical information is available for the prevention of AKI and very scant information for the other categories (Table 49-1).

Diuretics

Both loop diuretics and osmotic diuretics have been shown to decrease tubular oxygen demand and relieve intratubular obstruction in animals.[38] Intratubular obstruction with debris released from injured or dead tubular epithelial cells from more proximal parts of the nephron can cause back pressure to the glomerulus further limiting glomerular filtration.[39] This fact, combined with the widely held belief that nonoliguric AKI carries better outcomes, made the clinical use of diuretics (especially loop diuretics) in oliguric AKI popular until recent times.[40] More recent data has shown that both loop diuretics and osmotic diuretics are of limited use in attenuating the extent of the kidney injury or altering the outcomes in a positive manner.[3,41–44]

In a retrospective analysis of data from a cohort of 552 patients with AKI in the intensive care units of a university hospital, Mehta and his colleagues examined the effect of diuretic use on all-cause hospital mortality, nonrecovery of renal function, and the combined outcome of death or nonrecovery of renal function. In this cohort, about 59% of the patients had used diuretics and after adjustments for covariates and propensity scores, this group had a significantly higher risk of death or nonrecovery of renal function (OR, 1.77; 95% CI, 1.14 to 2.76). There have been additional systematic reviews or metaanalyses concerning the role of diuretics in this setting.[45–47] None of these showed that diuretics were of any benefit in reducing the incidence of AKI, mortality, or need for renal replacement therapy (RRT). There is even a possibility of increased risk of temporary deafness or tinnitus with higher doses of furosemide.[44] Some clinicians continue to use loop diuretics in patients with AKI with the purpose of preventing or treating fluid overload, especially in critically ill patients on those on ventilator support. Such use may be justified but should not be expected to prevent worsening of AKI, decrease the need for RRT or improve mortality rates.[24]

Antioxidants: N-Acetylcysteine, Vitamin C

N-Acetylcysteine (NAC) is a thiol containing antioxidant with experimental evidence of improved renal function in mouse (and rat) renal ischemia-reperfusion injury.[48–50] Because of positive early reports, it has been used as an intervention to prevent radiocontrast-induced AKI in high-risk populations.[51,52] Several randomized controlled clinical trials have been done subsequently to investigate the role of NAC in contrast-induced AKI and in the setting of prolonged hypotension (e.g., abdominal aortic surgery).[53–55] Results of many of these do not support those early reports of benefit and controversy still exists on the efficacy of NAC in this setting. A recent metaanalysis of 41 randomized

TABLE 49-1 Agents with Significant Existing Clinical Information

AGENT	CLINICAL EVIDENCE	COMMENTS	REFERENCES
Diuretics			
Loop diuretics	Negative	Not useful in improving mortality, but maybe useful in maintaining fluid balance in AKI	3,44,46,56
Osmotic diuretics	Negative	Not useful in improving mortality	24,41,42
Antioxidants			
N-Acetylcysteine	Conflicting	Some recommend its use in radiocontrast-induced AKI	51–57,60,62,63
Ascorbic acid (vitamin C)	Conflicting	Not enough evidence to support its use in the prevention of radiocontrast induced AKI	65,66
Vasoactive Agents			
Dopamine (low dose)	Negative	No proven role in prevention and treatment	82–88,115
Fenoldopam	Conflicting	No proven role in prevention and treatment	93,103–115
Vasopressin	Negative	Not enough evidence for a beneficial effect in sepsis (but maybe beneficial in subgroup with less septic shock)	130–134
Terlipressin	Positive	Maybe useful in bridging for transplantation in hepatorenal syndrome	131,133,134
Other			
Calcium channel antagonists	Conflicting	No proven role in prevention and treatment	159–163
Theophylline	Minimal	Possibly useful in decompensated cardiac failure	139–150
Atrial natriuretic peptide	Conflicting	No proven role in prevention and treatment. Lower doses may be beneficial by reducing hypotensive episodes	152–156
Insulin	Conflicting	Reasonable to optimize glucose control but to what degree is not established. Glucose in 140-180 mg/dl may be reasonable.	67,68,77,78

controlled trials with 6379 patients evaluated multiple therapeutic agents in high-risk patients who received radiocontrast.[56] This metaanalysis showed that, compared to hydration alone, NAC was the most effective agent at preventing radiocontrast-induced AKI of all the agents examined (egg theophylline, fenoldopam, dopamine, furosemide, mannitol, and bicarbonate). The authors noted, however, this conclusion to be "debatable" with several limitations of the study, mainly the inconsistent definition of "radiocontrast-induced nephropathy" as primary outcome in most of the trials.

Recently, Hoffmann and colleagues found that in healthy volunteers without AKI, NAC can reduce serum creatinine concentration (and eGFR) independent of an effect on true GFR as assessed by cystatin C (cys-C).[57] This effect may be accomplished through an effect of NAC affecting creatinine metabolism[58] or altering the tubular secretion of creatinine. Despite this suggestion, not all studies support the concept that NAC alters serum creatinine independent of GFR.[59]

The overall conclusion that can be reached with these studies and systematic reviews is that NAC has not been proven conclusively to be of any benefit in prevention of radiocontrast or ischemia induced AKI.[60–63] However, since NAC is a low cost agent with a very good safety profile (no major reports of harm), many continue to recommend it to prevent contrast induced AKI.[56] It should be emphasized that NAC should never take the place of intravenous (IV) hydration.

Ascorbic acid (Vitamin C), a scavenger of reactive oxygen species, is another antioxidant that has shown some promise in animal experiments.[48–50,64] Human studies using ascorbic acid to prevent radiocontrast-induced AKI are less conclusive. Spargias and associates randomized 238 patients with serum creatinine of 1.2 mg/dl and receiving nonemergent coronary angiography or intervention to receive 3 g of ascorbic acid or placebo about 2 hours before such procedures and then a second and third dose later in the day and the next morning.[65] Mean serum creatinine concentration increased significantly in the control group versus the intervention group (difference of 0.09 mg/dl; 95% CI, 0 to 0.17; $P = 0.049$). These differences, however, do not seem to be clinically significant. More recently, a large trial (the REMEDIAL trial) found that the combination of ascorbic acid and NAC was no better than NAC and saline.[66] Thus at this time, the evidence does not support the use of ascorbic acid in the prevention of radiocontrast-induced AKI.

Insulin

Insulin resistance and hyperglycemia are common in critically ill patients and intensive insulin therapy targeting blood glucose level between 80, and 110 mg/dl reduced mortality[67] the incidence of AKI.[67,68] It is well-known that IRI is greater in chronic hyperglycemia[69] and thought to be related to increased oxidative stress.[70,71] Furthermore, acute hyperglycemia exacerbates myocardial[72] and renal ischemia-perfusion injury.[73] The effects of insulin may relate to improvement glycemic control or be due to direct cellular effects of insulin. The relationship of hyperglycemia and adverse outcome in critically ill patients with AKI was recently also observed in subgroup analysis of PICARD study.[74] The mechanism for clinical benefit may relate to the direct metabolic and nonmetabolic effects of hyperglycemia. Endothelial dysfunction and subsequent hypercoagulation, and dyslipidemia, commonly observed in critically ill patients, can also be partially corrected by insulin independent of its blood glucose lowering effect.[75,76] However, despite these promising results, the effect of intensive insulin treatment in the setting of critically ill patients is still controversial.[77,78] Using intensive insulin treatment specifically to evaluate protection from AKI has not been tested and needs to be confirmed in appropriately powered randomized clinical trials.

Dopamine

Exogenous dopamine can bind to at least three types of receptors: the dopamine receptor, the ß-adrenoreceptor, and the α-adrenoreceptor.[79] Differences in these receptors' affinity for dopamine account for its distinct dose-response profile. Dopamine is a selective renal vasodilator at low doses (1-3 mcg/kg/min).[79] Cardiac output and renal perfusion pressure are also improved at different doses of dopamine.[80,81] The ability to improve RBF provided the rationale for its use in the prevention and treatment of AKI.[82] Many clinical studies have been done to investigate the effect of dopamine on the natural history of AKI. The results of many of these studies have been conflicting and also complicated by the frequent use of surrogate endpoints that are sometimes not clinically relevant. A few systematic reviews and metaanalyses have also been undertaken.[82–87] The overall conclusion is that low-dose dopamine has no proven role in prevention and treatment of AKI.[82–88]

Why has dopamine failed in clinical trials? This has been examined in several reports. Low-dose dopamine consistently causes renal vasodilatation in healthy adults, but this effect is often attenuated or absent in ill patients.[89,90] In other reports, dopamine reduced renal vascular resistance in patients without AKI but paradoxically increased resistance indices in patients with AKI.[87] Several factors may account for this, including unpredictable pharmacokinetics in critically ill patients, hypertensive arteriopathy, or counterregulatory effects of other vasoactive hormones, such as activity of the renin-angiotensin-aldosterone system (RAAS) or sympathetic nervous system. Both extracellular volume depletion and hypoxemia have been shown to abrogate the renal effects of dopamine.[91] Based on many studies, low-dose dopamine should not be used in the prevention of AKI.

Fenoldopam

Fenoldopam is a selective dopamine-1 receptor (DA1) agonist which has been shown, like dopamine, to cause renal arteriolar vasodilatation, leading to an increase in RBF and improvement in renal function while attenuating the decline in RBF and function in animals exposed to radiocontrast.[92,93] Fenoldopam results in peripheral and renal vasodilation and diuresis and natriuresis via stimulation of vascular and renal tubular DA1 receptors.[94,95] Studies in healthy, salt replete subjects have confirmed dose dependent increases in renal plasma flow, urine flow rate, and urinary sodium excretion without changes in GFR.[94,96–101] The lack

of increase in the GFR is secondary to parallel vasodilation of both afferent and efferent renal arterioles rendering intraglomerular pressure constant.[102] Animal studies have demonstrated fenoldopam to be markedly more potent than dopamine in decreasing renal vascular resistance and augmenting RBF.[95] Its relative potency, in conjunction with the absence of the potentially deleterious cardiac side effects characteristic of dopamine due to ß-adrenoreceptor stimulation, were the impetus for trials examining its potential to prevent and treat renal ischemia.

The clinical benefit in humans is inconclusive. Randomized controlled trials and metaanalyses of clinical trials conclude that there is no proven role for fenoldopam in prevention and treatment of AKI.[93,103–114] In two trials of radiocontrast induced nephropathy in which subjects were randomized to receive fenoldopam at 0.05 to 0.1 mcg/kg/min before exposure to the intravenous radiocontrast agent, the relative risk (RR) of developing AKI in the intervention (fenoldopam) group was 1.11 (RR, 0.8 to 1.53; 95% CI).[56] The inability to show a positive clinical benefit was thought to be due to an inability to give an effective "renal dose fenoldopam" in the previous studies by Teirstein and others.[115] In their randomized controlled crossover study, Teirstein's group of patients after coronary angiography received either intrarenal administration of fenoldopam with a bifurcated catheter or intravenous administration. The group receiving intrarenal fenoldopam had a significantly higher GFR (73.7± 3.1 vs. 62.6 ± 2.5 ml/min/1.73 m^2, respectively; $P = 0.0007$).[115] If eventually replicated, these very interesting results will be logistically difficult to use clinically.

Norepinephrine

AKI is often associated with hypotension in patients with concurrent clinical problems like sepsis or liver failure, especially in intensive care units. Attempts to maintain systemic blood pressure within limits that allow visceral organ perfusion (including autoregulation of RBF) are usually done with systemic vasoconstrictors.[116–118]

Norepinephrine effectively raises the systemic mean arterial blood pressure above 80 mmHg in many hypotensive states associated with vasodilation by stimulation of both α- and β-adrenergic receptors.[116] This effect on mean arterial pressure is dose related, and as such the dosage of the drug can be titrated for desired effect. Some studies have shown, however, that despite this desirable effect, there is often a less desirable decrease in splanchnic and vital organ blood flow (including kidneys).[119–121] Most of these older studies together with experimental data show that norepinephrine can be used to induce a reversible model of AKI—an observation that has discouraged its clinical use for AKI.[122,123] Some authors have argued that norepinephrine-induced renal hypoperfusion may not necessarily occur in sepsis or other vasodilated states and cite various animal experiments that support that mixed α- and β-adrenergic stimulation can increase RBF in such situations.[124–128] Anderson and colleagues used infusions of norepinephrine at clinically relevant doses of 0, 0.1, 0.2, and 0.4 µcg/kg/min in conscious dogs and measured the RBF with an electromagnetic flow probe.[129] Their findings showed that mean arterial pressure, RBF, and GFR all increased with increasing dosage of norepinephrine and renal vascular resistance decreased accordingly.[129] There is a need for clinical trials in humans that will give a reliable answer to the question of whether norepinephrine and the kidneys are "friends or foes."[117]

Vasopressin and Analogs

Arginine vasopressin (AVP) is an endogenous peptide hormone with vasopressor and antidiuretic properties historically used to treat bleeding from esophageal varices in cirrhotic patients and for diabetes insipidus.[130] Arginine vasopressin receptor 1A (AVPR1A), the first of three major receptor types for AVP, is found in vascular smooth muscle (and the brain, liver, and kidney). A relative deficiency of AVP has been demonstrated in patients with septic shock.[131] This has led to the use of low dose AVP infusions (about 0.01–0.03 units/min) as adjunctive support to catecholamines for vasoconstrictor effect in sepsis-related hypotension. The Vasopressin and Septic Shock Trial (VASST), a multicenter, randomized, double-blind study, assigned patients with septic shock and were receiving a minimum of norepinephrine 5 mcg/minute (open label) to receive in addition either low-dose vasopressin (0.01 to 0.03 units/min) or norepinephrine (5 to 15 mcg/min) with protocol titration to maintain a target blood pressure. The study showed no significant difference in the primary endpoint (mortality rate at 28 days) or any of the secondary outcomes when low dose vasopressin (0.3 units/min) was used along with catecholamine vasopressors.[132] In a subgroup analysis, vasopressin may be beneficial in subjects with less severe septic shock; the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%, $P = 0.05$).[132]

Terlipressin, a glycine vasopressin, is a 12-amino acid synthetic analog of AVP that is currently being considered by the U.S. Food and Drug Administration (FDA) as an orphan drug for the treatment of type 1 hepatorenal syndrome (HRS). Consequently, it is not yet available for clinical use in the United States (or elsewhere in North America), but it is already in use in Europe. Its major advantage is the long half-life of the drug that makes intermittent dosing (every 6 hours) possible, rather than a continuous infusion.[116] Two recent clinical trials have shown good results in cohorts of patients with AKI, specifically type 1 HRS.[133,134] Sanyal and associates evaluated the safety and efficacy of terlipressin for reversal of type 1 HRS in patients with cirrhosis in a prospective, randomized, double-blind, placebo-controlled clinical trial.[134] The treatment group (n=56) received terlipressin 1 mg intravenously every 6 hours (versus placebo, n=56) plus albumin in both groups. The results showed that terlipressin was superior to placebo for HRS reversal (34% vs. 13%, $P = 0.008$), and HRS reversal significantly improved survival at day 180.[134] Martin-Llahi and coworkers found similar results in HRS when IV terlipressin was added to IV albumin.[133]

Adenosine Analogs

Locally produced adenosine in the kidney controls renal circulation and metabolic cellular activity.[135] Four subtypes of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) are characterized

by having seven putative transmembrane-spanning domains, and they mediate a multitude of physiological responses.[136] Adenosine acts on these receptors in organs such as brain, heart, and skeletal muscle and induces vasodilation to allow matching of oxygen delivery and work.[135] Adenosine has been shown to be involved in the renal hemodynamic response to radiocontrast agents and the immune response to renal ischemia-reperfusion injury.[137,138] Theophylline, an adenosine A1-receptor antagonist, has been used successfully in several randomized controlled studies to prevent radiocontrast-induced AKI (as reviewed in references 139–141). Theophylline has been used in several case-control and randomized controlled studies as a potential prophylactic agent against radiocontrast-induced AKI.[139–144] A metaanalysis of these six studies shows discordant results with only four out of six studies with some evidence of reduction of relative risk of radiocontrast-induced AKI.[56] Other systemic reviews and opinions agree that the results have been discordant mainly with some consideration that it may be more useful in the cohort of preexisting decompensated cardiac failure.[56,140,145–150] Currently there is little convincing evidence for recommending theophylline in the prevention of radiocontrast-induced AKI.

Natriuretic Peptides

Atrial natriuretic peptide (ANP) has been shown to be beneficial in protection of radiocontrast associated AKI in animal studies.[151] Multiple large and multicenter randomized controlled studies have failed to show such clinical benefit, however.[152–154] A predetermined subgroup analysis in Allgren's earlier study in which subjects received anaritide, a 25-amino acid synthetic form of atrial natriuretic peptide[153] that suggested a possible benefit of dialysis-free survival in the oliguric cohort of patients, was not replicated in the later study.[154] One potential complicating feature of these studies was that too high of a dose of anaritide was used (200 ng/kg/min) causing hypotension in 94% of the anaritide group versus 45% of the placebo group.[153] A more recent smaller and single center randomized controlled trial in 61 patients undergoing cardiac surgery and using a continuous low-dose infusion (50 ng/kg/min) of recombinant natriuretic peptide showed benefit in dialysis-free survival and decreased need for dialysis versus the placebo group.[155] In this study the hypotensive episodes were similar (59% vs. 52%). A systematic review and metaanalysis of ANP in AKI found 19 randomized controlled trials (11 for prevention and eight for treatment).[156] The studies were described as low to moderate quality and mostly underpowered, and as such no definitive statements could be made about ANP use in AKI prevention or therapy.[156] Continuous low-dose infusion of ANP will need to be performed in larger clinical trials before it can be recommended for routine use.

Calcium Channel Antagonists

Calcium channel antagonists relieve afferent arteriolar vasoconstriction, among other actions, and have been shown to be protective against radiocontrast associated AKI in animals.[157,158] Calcium channel blockers have been used in different randomized controlled studies to assess ability to prevent AKI from radiocontrast and in renal allografts.[159–163] The preservation of GFR by day 2 in patients treated with nitrendipine versus placebo and exposed to radiocontrast study seems promising;[163] however, the others do not show any benefit of calcium channel blockers in this setting.[161,162]

Identification of effective pharmacological agents for the prevention and treatment of AKI remains a subject of intense focus for many investigators. None of the agents discussed have had enough impact to be considered sole and effective intervention for the prevention or treatment of AKI. Further large clinical trials may give more information on these agents and newer ones. Newer agents in early stages of investigation include activated protein C, growth factors, and adult stem cells.[164–167]

The proven preventive clinical strategies of good hydration and volume expansion with isotonic saline prior to exposure to radiocontrast agents, discontinuation of nonsteroidal anti-inflammatory agents, metformin, angiotensin-converting enzyme (ACE) inhibitors, limitation of nephrotoxin exposure, and efforts to maintain renal perfusion still remain very useful clinical strategies.

WHAT DRUGS ARE ON THE HORIZON?

A number of drugs and investigational compounds appear promising in preclinical studies (Table 49-2), and promising investigational compounds are in use in clinical trials for a variety of indications.

Antiapoptotic Drugs

Caspase Inhibitors

Caspases are a family of proteases involved in the initiation and execution phase of apoptosis. Nonselective and selective caspase inhibitors are effective in attenuating renal injury in ischemia- or endotoxemia-induced AKI when administered before or at the time of injury.[168–170] Pancaspase inhibitors are in early clinical trials,[171] and early targets include hepatitis C and orthotopic liver transplantation.

Minocycline

Minocyclines are second generation tetracycline antibiotics with proven human safety data. Minocycline is known to have antiapoptotic and antiinflammatory effects. When administered 36 hours before renal ischemia, minocycline reduced tubular cell apoptosis, mitochondrial release of cytochrome C, p53, and Bax.[172] Furthermore, minocycline reduced kidney inflammation and also microvascular permeability.[173] Minocycline has been used in clinical trials for rheumatoid arthritis[174] and amyotrophic lateral sclerosis.[175] Currently minocycline is being tested in AKI following cardiac surgery, acute spinal cord injury and acute stroke (see www.clinicaltrials.gov).

Pifithrin-α (p53 Inhibitor)

The tumor suppressor protein p53 is homotetrameric transcription factor and regulates cell cycle and apoptosis by inducing cell cycle arrest or apoptosis in response to DNA damage. A variety of factors induce activation of p53,

TABLE 49-2 Emerging Pharmacological Agents for Treatment of AKI

Antiapoptosis/necrosis agents
Caspase inhibitors
Minocycline
Pifithrin-a (p53 inhibitor)
Poly (ADP-ribose) polymerase (PARP) inhibitor
Antisepsis
Ethyl pyruvate
Activated protein C
Insulin
Growth factors
Recombinant erythropoietin
Hepatocyte growth factor (HGF)
Ghrelin
Bone morphogenic protein 7
Vasodilators
Carbon monoxide release compounds
Bilirubin
Endothelin antagonist
Antiinflammatory drugs
Sphingosine 1 phosphate analogs
Adenosine 2A agonists
Adenosine analogs
Inducible nitric oxide synthase (iNOS) inhibitors
Fibrates
Statins
Other agents
Neutrophil gelatinase-associated lipocalin
IL-6 and C5a antagonists
IL-10
Alpha melanocyte stimulating hormone

including irradiation, hypoxia, and nucleotide depletion.[176] Additional activities regulated by p53 are supported by studies including regulation of autophagy, glycolysis, repair of genotoxic damage, cell survival, regulation of oxidative stress, motility, cellular senescence, and differentiation.[176] Once activated, p53 induces apoptosis by activating proapoptotic Bax that triggers apoptosis via the intrinsic pathway. Pifithrin-α, a novel p53 inhibitor, downregulates activation of Bax and inhibits the translocation of p53 to mitochondria,[177] decreases tubule cell apoptosis, and preserves renal function.[178] In mice, cisplatin treatment induced p53 phosphorylation and acute kidney injury.[179] P53 was induced in both proximal and distal tubular nephron segments. In these mice subjected to cisplatin nephrotoxicity, Pifithrin-α attenuated p53 activation and reduced kidney injury during cisplatin treatment. Furthermore, cisplatin-induced nephrotoxicity was blocked in p53-deficient mice. Compared to wild-type animals, p53-deficient mice showed a better renal function, less tissue damage, and fewer apoptotic cells. This agent is currently being used in clinical trials in cancer therapy and is a target for the treatment of human AKI. Furthermore, siRNA to knock down p53 is in clinical trials for human AKI.[180]

Poly (Adenosine 5'-Diphosphate Ribose) Polymerase Inhibitor

Poly (adenosine 5'-diphosphate-ribose) polymerase (PARP) is a ubiquitous nuclear enzyme that participates in DNA repair.[181–183] Single-strand breaks in DNA activates PARP and catalyzes the transfer of adenosine diphosphate (ADP)-ribose moieties from oxidized nicotinamide adenine dinucleotide (NAD^+) to nuclear proteins including histones and PARP.[182,184] Paradoxically, excessive activation of PARP extends chains of ADP-ribose on nuclear proteins and results in intracellular NAD^+ and adenosine triphosphate (ATP) depletion, ultimately resulting in cell dysfunction and death.[182] PARP overactivation has been known to play a role in the pathogenesis of IRI to kidney, heart, and brain.[185–190] Organ injury is attenuated in mice in which the gene has been disrupted for PARP ($PARP^{(-/-)}$ mice).[188–190] Investigational compounds that act as chemical inhibitors have been long sought after, and different classes including benzamides and isoquinolinones have been proven effective but had weak inhibitory activities or biovailability.[191] Newer compounds (5-aminoisoquinolinone) with improved water solubility and potency have been proven to be effective in models of ischemia reperfusion injury of heart,[192] liver,[193] and hemorrhagic shock.[194] Intravenous inhibitors are currently in clinical trials for cancer therapy and in heart attack patients (completed) undergoing percutaneous coronary intervention.

Antisepsis Drugs

Ethyl Pyruvate

Pyruvate has been known as a potent endogenous antioxidant and free radical scavenger, and its derivative, ethyl pyruvate, proved to be effective in reducing mortality in animal models of lethal hemorrhagic shock and systemic inflammation caused by endotoxemia or sepsis.[195] In addition to an effect on mortality, ethyl pyruvate also reduced kidney injury in a cecal ligation puncture (CLP) model of sepsis.[196] Recently the antiinflammatory agent methyl-2-acetamidoacrylate (M2AA), a stable analog of ethyl pyruvate, was administered in a CLP model of sepsis.[197] M2AA improved survival and organ injury even if treatment was delayed by 6 hours. Reducing nuclear factor kappa B (NF-κB) activation contributes significantly to the mechanism of M2AA mediated tissue protection.

Thrombomodulin and Activated Protein C

Proteolytic activation of protein C occurs on the endothelial cell by two membrane receptors, thrombomodulin and endothelial protein C receptors (EPCR). Binding of thrombin to thrombomodulin on the endothelial surface promotes its anticoagulant properties by activation of protein C (APC) by the thrombin-thrombomodulin complex and is enhanced by binding of protein C to EPCR.[198] Additionally, soluble thrombomodulin independent of its ability to generate activated protein C reduced ischemia-reperfusion injury.[199]

In this study an aortic clamp model was used; soluble thrombomodulin (sTM) not only attenuated the rise in creatinine following reperfusion, but it also improved microvascular erythrocyte flow, reduced microvascular endothelial leukocyte adhesion, and minimized endothelial permeability. A mutant, F376L, in which a point mutation was made in sTM, reduced ischemia-reperfusion injury, suggesting that the protective effect of sTM is independent of its ability to generate activated protein C.

APC, in addition to its effect on coagulation, has been shown to have direct cellular effects via EPCRs including antiinflammatory and antiapoptotic activities, leukocyte activation, and stability of barrier function.[198,200–205] Through genetic engineering of wild type APC, mutants have been created that have cytoprotective effects of APC and anticoagulant activity.[206,207] Following endotoxemia, these molecules with preserved cytoprotective properties are effective in preserving RBF, attenuating acute kidney injury,[207] and reducing mortality.[208] On the other hand, an APC mutant with potent antithrombotic activity but minimal cytoprotection was less effective in reducing endotoxin-induced murine mortality.[209] Thus it is the hope that genetically engineered APC mutants and thrombomodulin might yield specific agents that take advantage of selective anticoagulant and cytoprotective properties in future clinical studies of AKI from sepsis or in critically ill patients.

Growth Factors

Recombinant Erythropoietin

The erythropoietin molecule is a glycoprotein with a molecular weight of 30.4 kDa. Binding of erythropoietin to its receptor on target tissue leads to homodimerization of the receptor and initiation of complex intracellular signaling pathways.[210–212] Exogenously administered erythropoietin, before or at the time of reperfusion reduced kidney injury by reducing tubular necrosis and apoptosis.[213–215] Recombinant erythropoietin has additional cell survival properties such as induction of phosphatidylinositol 3-kinase (PI3K)/Akt pathway[216] or heat shock protein 70.[217] Recombinant erythropoietin enhanced tubular proliferation in cisplatin-induced AKI[218] and also mediated mobilization and proliferation of endothelial progenitor cells (EPC) from the bone marrow that has been shown to participate tissue repair.[219,220] Recent studies have shed light on recombinant erythropoietin-erythropoietin receptor events mediating tissue protection that differs from hematopoietic effects. The tissue-protective effects of recombinant erythropoietin appear to require a physical association between the common [beta]-receptor chain subunit (CD131) and erythropoietin receptor.[221] Most recently the helix B (amino acid residues 58–82) of erythropoietin and an 11-aa peptide composed of adjacent amino acids of helix B was found to be tissue protective and without erythropoietic activity.[222] These results indicate that nonerythropoietic peptides of erythropoietin that simulate a portion of erythropoietin receptor's three-dimensional structure possess tissue-protective properties. Thus recombinant erythropoietin or nonerythropoietic peptides are agents that have promise in the treatment of AKI.

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is a mesenchyme-derived, polypeptide that is a potent mitogen for hepatocytes (reviewed in reference 222). Mature HGF is a heterodimeric molecule consisting of a 69 kDa a-chain and a 34 kDa b-chain. HGF is synthesized and secreted as a 728 aa single-chain precursor processed by specific serine proteases to generate a biologically active form that is made up of two chains.[223] HGF can promote cell growth, motility and morphogenesis and act as a cell survival factor.[224–227] Renal expression of HGF and its receptor, c-met, increases after IRI, and exogenous administration of HGF reduces renal injury and accelerates renal regeneration in a murine model of AKI.[228–230] The mechanism of protection is thought to involve a decrease in leukocyte-endothelial interaction with reduced inflammation and also a decrease in tubular cell apoptosis.[231]

Ghrelin, an endogenous ligand for growth hormone secretagogue receptor (GHSR),[232] is a peptide of 28 amino acids and is known to induce nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) by growth hormone and insulinlike growth factor 1 (IGF-1).[233,234] In rats subjected to ischemia-reperfusion injury, repeated doses of ghrelin administered prior to injury reduced injury.[235] However, if it was administered at just prior to ischemia and 8 hours later, no effect was observed. The protective effect of ghrelin administration was thought to be mediated by IGF-1.

Bone Morphogenic Protein

Bone morphogenetic proteins (BMP-7), are members of the transforming growth factor-[beta] superfamily that has been shown to be essential for cell growth, migration, and differentiation during development skeletal, kidney, and ocular development.[236] Renal IRI leads to decreased levels of BMP-7 messenger RNA in the rat kidney, primarily in the outer medulla and glomeruli at 6 hours, which is more pronounced at 16 hours.[237] Administration of exogenous BMP-7 1 hour and 16 hours following onset of reperfusion attenuates the severity of the injury.[238] BMP-7-treated proximal tubule cells block basal and TNF-α stimulated expression of the proinflammatory cytokines IL-6 and IL-1β, the chemokines monocyte chemotactic protein-1 (MCP-1) and IL-8, and endothelin 2 (ET-2).[239]

Vasodilators

Carbon Monoxide Release Compounds and Bilirubin

In a seminal study, Nath and associates found that heme oxygenase (HO) induction played a central role in limiting the extent of AKI.[240] HO activity leads to the production of carbon monoxide (CO) and a potent antioxidant bilirubin, and it is thought that the protective effect of HO activation is through these factors.[240,241] Administration of CO donor compounds tricarbonyldichlororuthenium(II) dimer, ([Ru(CO)^{3}l^2(2), or tricarbonylchloro(glycinato)ruthenium(II) ([Ru(CO)^{3}l(glycinate)]), (CORM-3) 1 hour before the onset of ischemia[242] or 24 hours prior to lipopolysaccharide

administration[243] reduced AKI. This suggests that CO itself may be protective and limit renal damage in AKI.[242] Bilirubin has also been shown to reduce kidney injury from IRI,[244] and when biliverdin and CO are used in combination, they are synergistic in improving heart allograft survival.[245] CO has a number of biological effects that could contribute to tissue protection including vasodilation, cell proliferation, anti-inflammation, and antiapoptosis.[246] Preconditioning by CO leads to a reduction of injury induced by ischemia-reperfusion injury[247] or cisplatin.[248] Carbon monoxide induces hypoxia inducible factor-1a (HIF-1a), which has a number of target genes including heme-oxygenase[249] that could lead to local tissue protection. Clinical applicability would necessitate the use of CO donors or the use of CO in therapeutic doses. Beneficial effects have been observed at doses as low as 10 parts per million (ppm) and up to 250 to 500 ppm in other animal studies. This dose is much lower than that used in pulmonary function testing (3000 ppm).[246]

Endothelin Antagonist

A potent vasoconstrictor, ET-1 has been implicated to play important roles in animal models of AKI or radiocontrast nephropathy.[250,251] ET-1 mediates its biological effects by binding to ET_A or ET_B receptors. In rat kidney, ET_A receptor stimulation is known to mediate vasoconstriction, while ET_B receptor activation can also mediate vasodilation by generation of NO and prostacyclin.[252,253] In addition, ET-1 can stimulate the expression of adhesion molecules and the production cytokines from monocytes and neutrophils, suggesting the possible role of ET-1 in inflammation in AKI.[254] Several studies demonstrated the beneficial effect of selective ET_A or nonselective endothelin receptor antagonist (ERA) in ischemic ARF, but the major limitation of those studies is the fact that ERA was administered before injury. Administration of the drug at later time point during the reperfusion was ineffective. However, Wilhelm and colleagues recently showed that tezosentan, a dual ET-1 receptor antagonist, attenuated renal injury even when administered after ischemia.[255]

Antiinflammatory Drugs

Inflammatory cells including polymorphonuclear cells, monocytes, macrophages and T-cells have received considerable attention as important contributors to ischemic acute renal failure. Several new compounds appear to be effective in reducing injury for ischemia-reperfusion through direct action on leukocytes.

Sphingosine 1 Phosphate Analogs

Sphingosine 1 phosphate (S1P) is a specific ligand for a family of G protein coupled endothelial differentiation gene (EDG) receptors (also referred to as S1PRs 1-5) that evoke diverse cellular signaling responses. S1PRs regulate different biological processes depending on their pattern of expression and the diverse G proteins present. S1P binds to receptors or acts as a second messenger to stimulate cell survival, inhibit cell apoptosis, and inhibit cell adhesion and movement.[256] An S1P analog, FTY720, acts as an agonist at four S1P receptors, which leads to sequestration of lymphocytes in secondary lymphatic tissue.[257] In studies of kidney IRI, FTY720 or similar compounds produced lymphopenia and renal tissue protection.[258,259] With discovery of new S1P analogs, more potent and selective agents will be available for preclinical and clinical studies.[260] Recently in a phase II study, FTY720 reduced the number of lesions detected on magnetic resonance imaging and clinical disease activity in patients with multiple sclerosis.[261]

A_{2A} Agonists and Other Adenosine Analogs

Adenosine binds to receptors that are members of the G-protein coupled receptor family that includes four subtypes: A_1R-, $A_{2A}R$-, $A_{2B}R$-, and A_3R.[262] Accumulating data demonstrate that selective activation of $A_{2A}Rs$ reduces parenchymal injury in nonrenal tissue including heart, liver, spinal cord, lung, and brain.[263–265] The selective A_{2A}-agonist, ATL146e, is highly protective against IRI of kidney and reduces injury by 70% to 80%.[266–268] Following administration either before or immediately at the onset of reperfusion, ATL146e alone or in combination with a phosphodiesterase inhibitor reduced renal injury.[269] ATL146e is in human clinical studies for cardiac imaging, and current efforts are directed toward human clinical studies in AKI. Additional studies demonstrate that strategies using A_1 agonists or A_3 blockers maybe effective in AKI.[270,271]

Inducible Nitric Oxide Synthase Inhibitors

The role of NO and nitric oxide synthases has been extensively studied. Both in vivo and in vitro studies point toward the important role of inducible nitric oxide synthase (iNOS) in mediating injury to proximal tubules.[272] Selective iNOS inhibitors are currently used in human investigation for a variety of indications.

Statins

3-Hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase inhibitors (statins) have been clinically approved for the reduction of cholesterol; however, this class of agents has properties that are independent of its cholesterol lowering effect, including antiinflammatory, antioxidant activities, improved endothelial function, decreased platelet aggregation, and procoagulation factors.[273–275] In rodent model of renal IRI, pravastatin was administered for 3 consecutive days and was shown to decrease the rise in plasma creatinine when compared to vehicle treatment without a change in plasma cholesterol levels.[276] When mevalonate, a product of HMG-CoA reductase, was coadministered on renal IRI, the protective effect was reversed, demonstrating that the tissue protective effect of pravastatin was to inhibit the mevalonate pathway. Similarly when simvastatin was administered 3 consecutive days prior to CLP induced sepsis, the rise in creatinine, TNF-α, and vascular permeability was attenuated.[277] These studies suggest the potential for a drug currently used in patients for the treatment of hypercholesterolemia to also be used in AKI.

Fibrates

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate glucose and lipid metabolism. PPAR-alpha is expressed in the renal proximal tubule, which upon activation, heterodimerizes with the

retinoic X receptor (RXR) and binds to PPAR response elements (PPRE) to regulate gene transcription involved in lipid metabolism.[278–280] When proximal tubule epithelial cells were exposed to cisplatin, the increase apoptosis was suppressed with bezafibrate.[281] The effect of bezafibrate to reduce apoptosis was associated with attenuation of cisplatin-induced translocation of proapoptotic Bax from the cytosol to the mitochondria and increase in the expression of antiapoptotic molecule Bcl-2.[281] Recent studies have indicated PPARs play an important role in inflammation and immunity.[282] Pretreatment of animals with WY-14, 643 (WY), a fibrate class of PPAR-alpha ligand ameliorated cisplatin induced renal dysfunction and this was accompanied by suppression of NF-κB activation, cytokine/chemokine expression and neutrophil infiltration, suggesting that the protective effect of fibrates is mediated through its anti-inflammatory effect.[283] Most recently, fibrates have been shown to increase liver fatty acid binding protein (L-FAPB) and decrease cisplatin induced acute kidney injury.

Other Compounds

Neutrophil gelatinase-associated lipocalin,[284] IL-6, and C5a antagonists,[285] IL-10,[286] and alpha melanocyte stimulating hormone[287] are other potential compounds that have multiple mechanisms of tissue protection and maybe beneficial in human AKI.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Bruce Molitoris (Indiana University) and Dr. Diane L. Rosin (University of Virginia) for helpful comments. This work was supported in part by funds from NIH (RO1DK56223, RO1DK62324 to MDO).

A full list of references are available at www.expertconsult.com.

Chapter 50

DIALYTIC MANAGEMENT FOR ACUTE RENAL FAILURE

Etienne Macedo, M.D., Glenn M. Chertow, M.D., M.P.H., and Ravindra L. Mehta, M.D.

The incidence of acute kidney injury (AKI) in hospitalized patients has varied from 5% to 20% in the past decade, depending on the definition and patient location.[1–3] Most critically ill patients develop AKI as part of multiple organ failure (MOF), and the complexity of illness in these patients has been progressively increasing. When dialysis is required, morbidity increases and mortality varies from 50% to 70%.[4–9] Since the 1960s, when intermittent hemodialysis (IHD) for the treatment of AKI became a common clinical tool for patients with severe AKI, dialytic options have expanded considerably. Biocompatible membranes, bicarbonate dialysate, and dialysis machines with volumetric ultrafiltration control have improved the treatment for AKI in the intensive care unit (ICU). Along with advances in methods of IHD, continuous renal replacement therapies (CRRTs), including hemofiltration and hemodiafiltration, have gained widespread acceptance in the treatment of dialysis-requiring AKI.[10–12]

The indications, timing of dialytic intervention, and the choice of dialysis modality are factors that appear to influence outcomes in AKI patients. This chapter outlines current concepts in the use of dialysis techniques for AKI and suggests an approach for selecting the optimal method of renal replacement therapy.

GOALS OF AND INDICATIONS FOR RENAL REPLACEMENT THERAPY

The treatment of AKI with renal replacement therapy (RRT) has the following goals: 1) to maintain fluid and electrolyte, acid-base and solute homeostasis; 2) to prevent further insults to the kidney; 3) to permit renal recovery; and 4) to allow other supportive measures (e.g., antibiotics, nutrition support) to proceed without limitation or complication. Ideally, therapeutic interventions should be designed to achieve those goals. In practice, the use of most dialytic modalities is based on physician preferences and experience. No evidence-based criteria have been established to guide modality choice, thereby making comparisons among centers or strategies at the same or different institutions difficult. An important consideration is to recognize that patients with AKI are distinct from those with end-stage renal disease (ESRD). The rapid decline of kidney function associated with MOF does not permit the adaptive responses that characterize the course of the patient with chronic kidney disease (CKD). Consequently, the traditional indications for renal replacement, developed for patients with advanced CKD, are not necessarily valid in this context. For instance, massive volume overload, resulting from volume resuscitation, a common strategy used for MOF, may be an indication for dialysis, even in the absence of significant elevations in blood urea nitrogen (BUN) or serum creatinine (SCr). In this instance, it may be more appropriate to consider dialytic intervention in the intensive care unit (ICU) patient as a form of renal support rather than renal replacement. Indeed, some of the traditional indications for dialysis (e.g., uremic pericarditis, pleuritis, or other serositis) would be considered "complications" of AKI rather than indications for dialysis. Table 50-1 lists several proposed indications for dialytic intervention using this approach. It is possible to widen the indications for dialytic intervention and provide a customized approach for the management of each patient.

TABLE 50-1 Potential Applications for Renal Replacement Therapy

RENAL REPLACEMENT	RENAL SUPPORT
Life-threatening indications	Nutrition
Hyperkalemia	Fluid removal in congestive heart failure
Acidemia	
Pulmonary edema	Cytokine manipulation in sepsis
Uremic complications	
Cancer chemotherapy	
Solute control	Treatment of respiratory acidosis in acute respiratory distress syndrome
Fluid removal	
Regulation of acid-base and electrolyte status	Fluid management in multiorgan failure

MODALITIES FOR RENAL REPLACEMENT THERAPY

Several methods of dialysis are available for RRT (Tables 50-2 and 50-3). Although most of these have been adapted from dialysis procedures developed for ESRD, several variations are available specifically for AKI patients.

TABLE 50-2 Dialysis Modalities for Acute Kidney Injury

Intermittent Therapies
Hemodialysis (HD)
Peritoneal (IPD)
Hemofiltration (IHF)
Ultrafiltration (UF)
Sustained low efficiency dialysis (SLED)
Extended daily dialysis (EDD)
Continuous Therapies
Peritoneal (CAPD, CCPD)
Ultrafiltration (CUF)
Hemofiltration (CVVH)
Hemodialysis (CVVHD)
Hemodiafiltration (CVVHDF)

Intermittent Procedures

Hemodialysis is based on the diffusion of solutes from the blood to the dialysate across a membrane driven by a concentration gradient between two compartments. The amount of solute transported per unit of time (clearance) depends on the molecular weight of the solute, the characteristics of the membrane, and the dialysate and blood flows.[13] IHD has been used widely for the past four decades to treat ESRD and AKI. It remains the most commonly used treatment modality for the management of AKI requiring RRT. Several important technological advances have made the procedure safer and better suited for the AKI patient. The availability of variable sodium concentrations in the dialysate, biocompatible membranes, bicarbonate-based dialysate, and volumetrically controlled ultrafiltration offer certain advantages to the AKI patient.[14,15] In ESRD patients, these machine enhancements have led to the development of a wide variety of different therapeutic regimens of IHD, including variations of high flux and high efficiency dialysis with high blood flow and dialysate flow rates.[16]

IHD has several advantages that have made this therapy widely used (Table 50-4). A short duration with rapid correction of electrolyte and acid-base disturbances and fluid removal provides the therapy great efficacy. The widespread availability of the machines and trained nurses allows the dialysis in AKI patients where machines for continuous therapies are not available. However, these features do contribute to some disadvantages. The limited time (usually 3-4 hours) limits renal support for the majority of the day during which controlled fluid regulation, acid-base balance, and electrolyte homeostasis are not possible. Patients with hemodynamic instability may not tolerate the high ultrafiltration rates necessary to achieve a targeted fluid balance. As a result, the occurrence of intradialytic hypotension is higher than with CRRT and may contribute to delayed renal recovery.[17] Nevertheless, Schortgen and colleagues found that implementation of strict guidelines for the management and prevention of intradialytic hypotension helped reduce the incidence of such episodes, but did not affect overall mortality.[18]

Intermittent hemodiafiltration (IHDF) uses convective and diffusive clearance for solute removal. IHDF is popular in Europe but has not been used extensively in the United States, mainly because of the high cost of the sterile hemofiltration solution (also known as *replacement fluid*). Recently, several modifications have been made to IHDF, including the provision of online preparation of sterile hemofiltration

TABLE 50-3 Renal Replacement Therapy: Comparison of Operational Characteristics

Access	VV	VV	VV	VV	VV
Plasma flow (ml/min)	100	100	100	100	200
Total effluent flow (L/day)	0	36-48	36-48	60-84	48-108
Dialysate flow (ml/min)	0	0	25-33.3	16-25	100-300
Prefilter hemofiltrate solution (ml/min)	0	25-33.3	0	25-33.3	0
Urea clearance (ml/min)	1.7*	25-33.3	25-33.3	41-58.3	N/A

CVVH, continuous veno venous hemofiltration; *CVVHD,* continuous veno venous hemodialysis; *CVVHDF,* continuous veno venous hemodiafiltration; *EDD,* extended daily dialysis; *IHD,* intermittent hemodialysis; *SLED,* sustained low efficiency dialysis; *VV,* veno venous
*At ultrafiltration rate of 100 ml/hr.
(Modified from R.L. Mehta, Renal replacement therapy for acute renal failure: matching the method to the patient, Semin. Dial. 6 (1993) 253-259.)

TABLE 50-4 Comparison of Operational Characteristics, Advantages, and Disadvantages of Replacement Therapy Affecting Dialysis Prescription and Dose Delivered

PATIENT FACTORS	IHD	EDD	SLED	CRRT	PD
Hemodynamic tolerability	+++	+++	+++	+	+++
Patient mobility	+++	++	++	–	+
Intracranial hypertension	–	+	+	+++	+++
TECHNIQUE FACTORS	**IHD**	**EDD**	**SLED**	**CRRT**	**PD**
High blood flow	+++	++	++	++	NA
Short duration	+++	++	++	+	+
Recirculation	+++	++	++	+	NA
Anticoagulation	+	++	++	+++	–
Membrane clotting	+	+	+	+++	–
Ultrafiltration control	+	++	++	+++	+
Rapid poison or potassium removal	+++	++	++	++	+
Infection potential	+	++	++	+++	++
OTHER FACTORS	**IHD**	**EDD**	**SLED**	**CRRT**	**PD**
Nursing errors	+	+	+	+++	+
Nursing support	+	+	+	+++	++
Simplicity	+	++	++	+++	+
Cost	+	++	++	+++	+

CCRT, continuous renal replacement therapy; *EDD,* extended daily dialysis; *IHD,* intermittent hemodialysis; *PD,* peritoneal dialysis; *SLED,* sustained low efficiency dialysis.

solutions. Proponents of this modality claim a greater degree of hemodynamic stability and improved clearance of middle molecule (i.e., molecules in the range of 500-60,000 Da, relatively poorly cleared with diffusive dialysis).[19]

Intermittent ultrafiltration (UF), in contrast to IHDF, can be done with the same machines as IHD but is used specifically for volume removal alone with minimal solute clearance. Most nephrologists use UF as a method of rapid fluid removal when the major indication for renal replacement or support is pulmonary edema or refractory congestive cardiomyopathy. In most instances where clearance is required, UF requires supplementation with IHD. Some centers use a combination of UF and IHD in the same session (*sequential ultrafiltration-hemodialysis*). This strategy offers a greater degree of hemodynamic stability resulting from the dissociation of solute and fluid removal during the dialysis. The improved hemodynamic status may be related to the attenuation of osmotic flux during the UF phase. Although sequential UF-IHD can be easily implemented, a major potential disadvantage of this strategy is the reduction in time for diffusive solute clearance. Since solute removal during UF alone is minimal, the treatment may be inadequate unless the overall treatment time is extended.

Sustained Low Efficiency Dialysis or Extended Daily Dialysis

In 1999, Schlaeper and colleagues[20] reported the use of slow continuous dialysis in which blood flow rates (Q_b) were 100 to 200 ml/min and dialysate flow rates (Q_d) were 100 to 300 ml/min. Patients were treated for 12 hours during the day or evening. Extended daily dialysis (EDD) was initially described by Kumar and colleagues[21] using lower blood and dialysate rates as sustained low efficiency dialysis (SLED), but also performed daily. EDD or SLED differs from IHD in that Q_b and Q_d are intentionally kept low but the duration of the treatment is extended. These hybrid modalities have been performed at night for 8 to 12 hours using ICU staff, thereby eliminating interruption of therapy, reducing staff requirements, and avoiding scheduling conflicts. Studies comparing hybrid modalities to CRRT have revealed favorable hemodynamic tolerance in critically ill patients while achieving dialysis adequacy and ultrafiltration targets, since fluid removal and solute clearance are more gradual.[22–26] Marshall and colleagues[27] showed that SLED can be a viable alternative to CRRT in critically ill patients who failed attempts at IHD because of hemodynamic intolerance. The use of standard IHD machines allows some cost savings by eliminating the need for special dialysate or hemofiltration solution. Anticoagulation use also has been shown to be less in SLED when compared to CRRT because SLED can be done without anticoagulation (saline flushes are possible since ultrafiltration can be extended).

The major advantages of SLED and EDD include the ability to provide as good or better hemodynamic and solute control as IHD, less intensive monitoring required by dialysis nurses and ICU staff, minimal training of nurses and support staff (in contrast to CRRT), and sufficient time for patient procedures requiring mobility.[21]

Continuous Techniques

Peritoneal Dialysis

Although the concept of continuous hemodialysis was advocated as early as 1960 by Scribner and colleagues,[28] peritoneal dialysis (PD) was the first form of CRRT. In PD, the patient's peritoneum acts as the semipermeable dialysis membrane. Dialysate consists of a sterile, lactate-based

solution inserted via a peritoneal catheter into the abdominal cavity. Diffusion occurs from peritoneum vessels perfused by the fluid in the abdominal cavity. Once the dialysate becomes saturated (generally within 3-4 hours, depending on peritoneal membrane transport characteristics), it is removed and replaced by fresh dialysate. Fluid removal is achieved by using an osmotic pressure mechanism in which varying dextrose concentrations in the dialysate provide an osmotic gradient for water flow from the patient's blood to the peritoneum. The procedure can be performed intermittently but is fairly labor intensive and is best done by personnel trained in PD procedures. More commonly, a variation of the procedure for continuous ambulatory PD termed *continuous equilibrated PD (CEPD)* is used.[29] The process can be less labor-intensive by using an automated cycler device that is programmed to deliver a fixed volume of dialysate and draining the peritoneal cavity at fixed intervals. However, cyclic PD suffers from the two basic problems as follows: 1) the procedure is relatively inefficient, and total solute removal is limited by the amount of peritoneal effluent; and 2) peritoneal transport characteristics may be altered with hypotension and pressor agents. For instance, in the hypercatabolic postoperative patient or patient with sepsis, PD may not provide the required amount of solute removal for adequate control of azotemia. The main advantages of PD are that it tends to be well-tolerated hemodynamically, allows much more gradual ultrafiltration relative to IHD, and does not require anticoagulation.

In adults, acute PD is infrequently used. The requirement of surgical insertion of the catheter associated with frequent malfunction and leakage are common considerations that lead to the avoidance of use of the peritoneum. Bedside placement of a temporary PD catheter is frequently complicated by infection; moreover, few nephrologists in the United States are adequately experienced with the technique. Moreover, instilling fluid in the peritoneal cavity may increase intraabdominal pressure; in patients presenting respiratory insufficiency, this increase in pressure may compromise lung function.

One prospective study in Vietnam compared PD and CRRT in critically ill patients to AKI due to either malaria or sepsis.[30] Seventy patients were randomly assigned to either PD or continuous veno venous hemofiltration (CVVH). The risk of death was much higher in the group assigned to PD (47% vs. 15%; odds ratio [OR], 5.1; 95% confidence interval [CI], 1.6 to 16), adjusting for underlying disease (malaria or bacterial sepsis, and the presence or absence of jaundice). In this study, the mortality rate for patients on CVVH was unusually low and PD was not performed using the most recent technological advances: use of bicarbonate (not acetate) in the dialysate and soft catheters.

Despite the concerns about its inadequacy, PD is widely used for AKI in developing countries. A prospective study performed on 30 AKI patients assigned to high-dose continuous PD (Kt/V = 0.65 per session) showed that high-dose continuous PD by flexible catheter and cycler provided high solute removal, allowing appropriate metabolic and pH control and adequate dialysis dose and fluid removal.[31] A prospective randomized controlled trial performed by the same group in Brazil[32] compared the effect of high volume peritoneal dialysis (HVPD) and daily hemodialysis (DHD) on AKI patient survival. A total of 120 patients with acute tubular necrosis (ATN) were assigned to HVPD or DHD, weekly delivered Kt/V was 3.67 in HVPD and 4.77 in DHD ($P = 0.01$). Metabolic control, mortality rate (58% and 53%), and renal function recovery (28% and 26%) were similar in both groups, whereas HVPD was associated with a significantly shorter time to the recovery of renal function.

In the pediatric population, intermittent peritoneal dialysis (IPD) continues to occupy a niche for RRT in AKI. In these patients vascular access is a challenge; therefore, PD rather than hemodialysis or CRRT is the first choice, particularly in newborns and infants.[33] The small body surface area allows for an adequate clearance without a large number of exchanges.[34]

Continuous Renal Replacement Therapies CRRT was introduced in the early 1980s to offer treatment for hemodynamically unstable patients. Over the past decade, these therapies have markedly evolved. The techniques differ principally in the driving force for solute removal and membrane used. When arteriovenous (AV) circuits were employed, the mean arterial pressure provided the pumping force. After the widespread use of veno venous (VV) catheters, the use of external pumps allowed for more precision in blood flow rates and transmembrane pressure. Removal of solutes in CRRT can be achieved by convection (hemodialysis), diffusion (hemofiltration [HF]), or the combination of the two methods (hemodiafiltration [HDF]). Diffusive clearance is more effective for small molecular weight solutes such as potassium, urea, and creatinine. Solutes with higher molecular weight (between 500 to 60,000 Da), so-called "middle molecules," are better removed by convection, where hydrostatic pressure provides the driving force for plasma across a membrane. While UF implies fluid removal only, HF necessitates partial or complete replacement of the fluid removed. The composition of the hemofiltration solution can vary, and the solution can be infused pre- or postfilter.

Diffusion techniques applied continuously are based on the same principles of solute gradients between the blood and the dialysate, as with IHD. However, unlike IHD, the dialysate flow rates (typically 0.5 to 2 L/hr, or 8-34 ml/min) in continuous hemodialysis are significantly slower than the blood flow rates (typically 100-200 ml/min), resulting in complete or near-complete saturation of the dialysate. Small molecules are preferentially removed by diffusion-based methods. If both diffusion and convection are used in the same technique, the process is termed *hemodiafiltration* (HDF). With HDF, both dialysate and hemofiltration ("replacement") solutions are used, and small and middle molecules can both be efficiently removed. The letters UF, H, HD, and HDF serve to identify the operational characteristics in the terminology. As shown in Table 50-2, the letter C in all terms describes the continuous nature of the methods, and the remaining letters (UF, H, HD, and HDF) represent the operational characteristics.

Conceptually, it is important to recognize that CRRT techniques are operationally very different from intermittent techniques, as shown in Table 50-3. The major difference is that time is no longer a limiting factor for blood purification; therefore, it is possible to use slower blood and dialysate flow rates and achieve weekly clearances that may be superior to intermittent techniques. Another major distinction is the ability to dissociate solute removal from fluid balance. For example, by varying the composition of the dialysate,

hemofiltrate, or both, solute balance can be altered, while fluid balance over time can be kept negative, positive, or even. While all the dialysis modalities can efficiently remove fluid and solutes, the available time for therapy is often a limiting factor. CRRT and SLED-EDD provide a greater opportunity to achieve fluid and solute balance over time.[35] Because transitions between therapies reflects patients' progression in the disease course, all the therapies should be considered as part of the nephrologist's armamentarium and used to support patients through their course (Table 50-5).

TIMING OF DIALYTIC INTERVENTION

Whether or not to provide dialytic support and when to start are two of the fundamental questions facing nephrologists and other intensivists in most cases of severe AKI. The optimal timing of dialysis for AKI is not defined. The association of early initiation of dialysis with survival benefit was first suggested by case series with historical controls conducted in the 1960s and 1970s.[36–39] However, given that BUN concentrations at the start of dialysis in the "early" treatment groups in these previous studies were high by modern standards, the relevance of these studies to current practice is questionable. In the modern dialysis era, few studies have examined the association of the timing of initiation of dialysis in AKI with mortality. Moreover, changes in illness severity, especially in later years, make comparisons of studies extremely difficult. Single-center studies that were restricted to AKI after trauma[40] and coronary artery bypass surgery[41,42] suggested a benefit to dialysis initiation at lower BUN concentrations. In a broader population of critically ill, Bouman and colleagues[43] randomized 106 critically ill patients with AKI to early versus late initiation of dialysis. The early initiation group started dialysis within 12 hours of low urine output, less than 30 ml/hr for 6 hours, not responding to diuretics or hemodynamic optimization, or creatinine clearance less than 20 ml/min. Late initiation started dialysis when classic indications were met. Although underpowered to detect survival differences, the study did not find differences in ICU or hospital mortality between the interventions groups or in renal recovery among survivors. A prospective multicenter observational cohort study[44] performed by the Program to Improve Care in Acute Renal Disease (PICARD) analyzed dialysis initiation—as inferred by BUN concentration—in 243 patients from five geographically and ethnically diverse clinical sites. Survival rates were slightly lower for patients who started dialysis at higher BUN concentrations, despite a lesser burden of organ system failure. Adjusting for age, hepatic failure, sepsis, thrombocytopenia, and SCr and stratified by site and initial dialysis modality, initiation of dialysis at higher BUN was associated with an 85% (95% CI, 16% to 196%) increased risk of death. The relative risk for death that was associated with initiation of dialysis at a higher BUN was 1.85 (95% CI, 1.16 to 2.96).

Although the maintenance of BUN concentrations below arbitrarily set levels is usually a reference for starting dialysis treatment, BUN reflects factors not directly associated with kidney function, such as catabolic rate and volume status. SCr is influenced by age, race, muscle mass, and catabolic rate, and its volume of distribution varies on fluid overload patients. Thus neither creatinine nor BUN should be used to absolutely determine when to initiate dialysis. In a prospective multicenter observational study conducted at 54 ICUs in 23 countries,[45] timing of RRT was stratified into "early" or "late" by median urea at the time RRT started and also categorized temporally from ICU admission into early (less than 2 days), delayed (between 2 and 5 days), or late (more than 5 days). Timing by serum urea showed no significant difference in mortality (63.4% for urea = 24.2 mmol/L vs. 61.4% for urea >24.2 mmol/L). However, when timing was analyzed in relation to ICU admission, late RRT was associated with greater crude mortality (72.8% late vs. 62.3% delayed vs. 59% early; $P = 0.001$) and covariate-adjusted mortality (OR, 1.95; 95% CI, 1.30 to 2.92; $P = 0.001$). Overall, late RRT was associated with a longer duration of RRT and a longer stay in hospital and greater dialysis dependence.

There are potential safety concerns regarding earlier initiation of dialysis, including increased risk for infection from an indwelling dialysis catheter, hypotension, potential for delayed renal recovery, and leukocyte activation from contact with dialysis membranes, among others.[46,47] The concept that dialysis initiation would prolong the course of AKI was supported by experimental data showing renal lesions consistent with fresh ischemia in dialyzed animals without systemic hypotension long after their initial renal injury. In the presence of ischemia, the vasculature of normal kidneys responds with vasodilation as part of the autoregulatory response to maintain renal blood flow (RBF) and glomerular filtration rate (GFR). In ATN, autoregulation is impaired; as a result, recurrent ischemic tubular injury is more likely to occur, thereby delaying the restoration of function.[48–50] However, it is difficult to document that earlier initiation of dialysis is of harm because patients with more severe forms of renal injury may develop indications for dialysis earlier in their ICU course and may be more likely to develop irreversible disease independent of therapy. Several factors can influence the survival and recovery of renal function in dialytic AKI patients. Whether these risks outweigh the potential benefits of earlier initiation of dialysis still is unclear.[47]

In current practice, the decision to dialyze is based most often on clinical features of volume overload and biochemical features of solute imbalance (e.g., azotemia, hyperkalemia). Data from a randomized controlled trial comparing IHD to CRRT suggest that the indication for dialysis is an important determinant of outcome.[51] In this study, patients dialyzed predominantly for solute control experienced better

TABLE 50-5 Transition Between Modalities in Observational and Randomized Clinical Trials

STUDY (REFERENCE)	CRRT TO IHD	IHD TO CRRT
Mehta, 2002[167]	18%	20%
Augustine, 2004[140]	15%	22%
Mehta, (PICARD) 2004[5]	24%	40%
Uchino, 2005[8]	9%	18.2%
Vinsonneau, 2006[138]	26%	73%
Palevsky, 2008[17]	57%*	

CCRT, continuous renal replacement therapy; *IHD*, intermittent hemodialysis.
*Transition between modalities including CRRT to IHD and IHD to CRRT.

outcomes than those dialyzed predominantly for volume overload. Patients dialyzed for control of both azotemia and volume overload experienced the worst outcome. In critically ill patients, especially in the postoperative period and in septic patients after volume expansion, the increase in total body water can reach more than 10 L within 7 days.[52,53] Mukau and colleagues[54] found that 95% of their patients with postoperative AKI had fluid excess of more than 10 L at the time of dialysis. The amount of fluid overload was a strong independent determinant of outcome. Volume resuscitation is a common strategy used in the treatment of MOF, particularly when accompanied by sepsis syndrome and hypotension. It is often applied indiscriminately in the setting of oliguric AKI, where it is assumed that providing additional volume will improve renal perfusion, prompting correction of renal dysfunction. Although this may be of great benefit to patients with prerenal azotemia, excessive volume administration can lead to pulmonary edema, compromising oxygenation and ventilation and hastening the need for dialysis. Despite recent evidence suggesting positive fluid balance as possibly harmful for ICU patients, the association between fluid balance and outcomes in AKI patients is not completely defined. These patients are expected to present higher positive fluid balance; however, the impact in the prognosis is poorly understood. Payen and associates[55] extracted data from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, a multicenter observational cohort study including 198 ICUs. In AKI patients, mean daily fluid balance was significantly more positive among nonsurvivors than survivors (0.98 ± 1.5 vs. 0.15 ± 1.06 L/24 hr, $P < 0.001$).

These factors collectively suggest the need to develop evidence-based, patient-specific, and nonbiased indications for the initiation of dialysis in AKI. Timing of RRT, a potentially modifiable factor, might exert an important influence on patient survival. However, it largely depended on its definition. We favor using an approach that recognizes that the strategy in treating AKI is to minimize and avoid uremic and volume overload complications. Thus it is not necessary (and arguably harmful) to wait for progressive uremia to initiate dialytic support. As discussed earlier, the indications for dialysis should include a consideration of the need for renal support (and renal replacement), and the timing of dialysis should be based on the goals to be achieved.

SELECTION OF DIALYSIS MODALITY

Patient Factors

Access

The availability of appropriate venous angioaccess is crucial for IHD and CRRT (CVVH, D, or HDF); an intraperitoneal catheter is required for PD. A variety of vascular catheters is now available that prevents the need for surgically placed central venous catheters and can sustain blood flows consistently above 300 L/min. If vascular access cannot be obtained, PD may be the only alternative, particularly in the pediatric patient.

The type of catheter and the technique of insertion are important to minimize complications. Access-placement-related complications depend on the expertise of the operator and are exacerbated by underlying coagulopathy.[56] Late complications include infection, thrombosis, and stenosis. These complications are associated with site of insertion and properties of catheter material. There may be a higher risk of bacteremia in femoral than jugular venous catheters,[57] but a recent randomized controlled trial of 750 patients with AKI requiring RRT found comparable rates of catheter colonization, bacteremia, and thrombosis between the jugular and femoral access sites.[58] In this study, the relative risk of catheter colonization between the jugular and femoral sites appeared to depend on patient body mass index (BMI): at high BMI, femoral catheters had higher rates of colonization, whereas at lower BMI, jugular venous catheters appeared to have higher rates of colonization.

Because the catheter is in direct contact with the bloodstream, its surface becomes coated with platelets, plasma, and tissue proteins such as albumin, fibrinogen, and fibronectin. These materials act as conditioning films where microorganisms can attach to the surface and form biofilms.[59] These microorganisms can come either by catheter skin exit site, the catheter tunnel, or through the intraluminal path, due to contamination of the catheter hubs. The intraluminal biofilm formation is considered a major source of catheter related bacteremia and the principle cause of antibiotic treatment resistance. Different surface treatment technologies, such as silver base coatings, are now being used to reduce the infection rate and also the thrombogenicity of catheters.[60,61]

In spite of the development of new catheter material and placement techniques, thrombosis of the subclavian vein has been increasingly recognized as a serious complication.[62,63] The incidence of this complication is difficult to establish, because only a few studies have been systematically performed. Stricture in the subclavian vein previously used for temporary dialysis is also a concern for patients who fail to recover after AKI, and require long-term dialysis. In a retrospective study involving 52 patients, after 2 years of catheterization, venograms demonstrated a 50% incidence of long-term venous stricture. No significant venous stricture was demonstrated along the course of the cannula in patients with previous internal jugular vein catheters.[64] In this context we recommend that the subclavian vein be avoided for catheter placement in AKI patients.[65,66] Often this may not be feasible, because there are limited sites for vascular access. In this case, whichever site is available and most easily cannulated should be used.

Blood recirculation in venous catheters is an important factor that contributes to a lower deliver dialysis dose in AKI patients. The arterial port of the catheter can extract part of the blood that was just delivered by the venous port. This recirculation is accentuated in short catheters, where up to 23% of the blood flow may recirculate.[67]

Requirement for Mobility

A major consideration in the choice of modality is the requirement of patient mobility. If patients are to be moved for different investigations—trips to the operating room for different procedures—it becomes more difficult to perform continuous therapies. The location of the patient (ICU or non-ICU) is an additional determinant of therapy because CRRT requires a higher nurse-to-patient ratio.[68]

Anticipated Duration of Treatment

Renal replacement for AKI is based on the premise that eventually there will be a return of kidney function allowing discontinuation of dialysis. Although this is the desired outcome, it does not always occur. This is particularly true for the patient with AKI complicating MOF, wherein the ultimate prognosis depends on recovery of other organ systems. Traditional teaching suggests that most patients with AKI will improve within 4 to 6 weeks, and a dialysis requirement beyond this period likely represents chronicity. Although this can be true in most instances, the following two important factors need to be considered: 1) some patients with AKI in the ICU setting may require prolonged dialysis support (>8 weeks) before recovering kidney function; and 2) recovery may be incomplete. The majority of studies addressing renal recovery include only critically ill patients requiring dialysis and consider renal recovery as freedom from dialysis at hospital discharge.[69] However, a large fraction of patients with AKI are not dialyzed and may require alternate definitions for assessing recovery of kidney function. There is emerging evidence that an AKI episode can lead to CKD and can accelerate the progression of CKD to ESRD. Patients who survive after AKI experience a higher long-term mortality risk, especially those with partial renal recovery.[70,71]

The duration of dialytic support may need to be predefined in some patients with AKI when other organ system failure accompanies AKI. For instance, a patient with respiratory, cardiac, and liver failure secondary to sepsis requiring dialytic support for AKI should have a finite (1-2 weeks) trial period of dialysis and be reassessed for evidence of improvement in all organ systems. Withdrawal of dialysis should be considered in selected patients with severe AKI accompanying MOF who are extremely unlikely to recover nonrenal organ function.

Modality-Specific Factors

Components

Choice of Membrane One of the key components of any dialysis system is the membrane, or *artificial kidney*. In addition to the well-recognized effects of membranes on solute and fluid removal, two additional factors must be considered in the choice of membranes for renal replacement in AKI.

Biocompatibility Membrane interactions leading to complement activation and neutrophil sequestration have been described predominantly for IHD.[72] However, the exposure time to the membrane is considerably greater in continuous therapy, and membrane effects may also influence outcome in CRRT. Newer membranes with heparin bonding[73,74] appear promising, although they have been associated with increased complement activation.[75,76] Cytokine induction can also occur during dialysis and may be related to the passage of endotoxin fragments across the membrane from the dialysate.[77] Use of *ultrapure* dialysate (dialysate that has been passed through additional filters after water purification) has been found to markedly reduce production of tumor necrosis factor α (TNF-α).[78,79] Additionally, the role of various soluble receptors and natural antagonists to cytokines in this setting is still unclear.[80,81]

Two conflicting metaanalyses were published in 2002, both reviewing trials comparing biocompatible (BCM) and bioincompatible (BICM) membranes and mortality. In the first metaanalysis, 722 patients were examined; the overall death rate was not different among patients treated with BCM and BICM (45% vs. 46%). Using a random effects model, a more conservative model for combining data that incorporates both within and between study variability, the relative risk of death was not significantly lower among patients dialyzed with BCM (relative risk [RR] = 0.92; 95% CI, 0.76 to 1.13; $P = 0.44$).[82] The second metaanalysis added one study that markedly affected the overall result.[83] This study was an observational study of patients with AKI, where dialysis modality was not limited to IHD, and where dialysis membrane use reflected the practice pattern of the participating centers. Further, it contributed more patients than any other study in the metaanalysis (n = 169).[84] The inclusion of this study carried significant weight in the compiled metaanalysis, resulting in a statistically significant overall lower relative risk of death among patients dialyzed with BCM compared to BICM (RR = 0.73; 95% CI, 0.55 to 0.98; $P = 0.03$). Neither metaanalysis demonstrated an overall effect of dialysis membranes on recovery of renal function.

Four trials have already compared the use of high-flux versus low-flux membranes in IHD.[85–88] No difference in mortality or nonrecovery of kidney function was found.

Cytokine Modulation CRRT using hemofiltration techniques may have an immunomodulatory effect. Some of the inflammatory mediators are water soluble cytokines: interleukin (IL) 6, IL-8, IL-1, and TNF. Theoretically, cytokines can be removed by convection according to their molecular weight and degree of plasma protein binding. The membrane characteristics such as molecular weight cutoff, structure and charge also affects the sieving coefficient (i.e., ability of a solute to convectively cross a membrane), and the adsorption capacity. Adsorption of inflammatory mediators by the membrane structure is also an important contributor to their clearance.[89]

In spite of some encouraging results, the clinical benefit of conventional CRRT in sepsis has been disappointing.[90] Consequently, efforts have been made to improve the efficiency of soluble mediator removal by increasing ultrafiltration rates and enlarging the pore size of membranes. In a pilot study, Morgera and colleagues[91] showed a beneficial effect using high cutoff membrane (molecular weight range of up to 60 kDa) for hemofiltration. Clearance rates for IL-6 and IL-1ra were significantly higher in the high cutoff hemofiltration group ($P < 0.0001$). In a randomized, prospective study on the effect of coupled plasma filtration-adsorption (CPFA) in human septic shock, Ronco and associates[92] showed that the increase in mean arterial pressure was significantly higher with CPFA than with conventional mixed convective-diffusive continuous therapy (CVVHDF). Clinical trials examining the safety and efficacy of new therapies should be performed.

The ongoing IVOIRE study (High Volume in Intensive Care) is designed to compare the effect of very high and high dosage of dialysis (70 and 35 ml/kg/hr) associated with frequent filter change on mortality at 28 days in patients with AKI and septic shock. This study will provide the first large evidence-based data on the relevance of very high

dosages of hemofiltration in AKI patients with septic shock[93] and might resolve the debate on the relevance of middle molecules clearance in AKI.

Dialysate Composition

IHD uses a dialysate produced by the dialysis machine by mixing treated water with electrolytes. Water purification treatment is a process that involves reverse osmosis, deionization, and use of charcoal filters. Diffusive procedures do not require sterile solutions because there is no direct contact between blood and dialysate. However, using high permeability membranes, lower blood side pressures at the end of the dialyzer filter may allow back-filtration of dialysate to the blood,[94] raising the possibility of endotoxin or other contaminant exposure. For CRRT, where Q_d is much slower than in IHD, dialysate needs to be produced locally in the hospital pharmacy or purchased, and the replacement fluid needs to be sterile. In ICU patients bicarbonate based solutions are used more frequently, considering the limited capacity to convert lactate to bicarbonate in patients with MOF.[95] Barenbrock and colleagues[96] compared the use of bicarbonate versus lactate in CRRT. They showed significantly reduced cardiovascular events in patients treated with bicarbonate compared with lactate as a buffer (RR, 0.39; 95% CI, 0.2 to 0.79), although these results need to be confirmed.

Bacterial contamination of the dialysate is a known problem in chronic patients. In CRRT, the prolonged time of the treatment and the use of locally prepared solutions pose additional hazards for bacterial contamination. The presence of various components in the CRRT circuit and the frequent need for set-up and maintenance are additional risks factors. Kanagasundaram and associates[97] found a frequent incidence of bacterial contamination in CVVHD bicarbonate based dialysate circuits. The study showed that the sterility of manufactured dialysate or hemofiltration solutions does not prevent its contamination when delivered through a contaminated circuit. A subsequent study of the same group evaluated culture and endotoxin assays of replacement fluid, culture of endoluminal swabs, and electron microscopy of harvested tubing at completion of therapy in 24 CVVH circuits. They found evidence of biofilm formation in more than 50% of the circuits. These studies confirmed the presence of unacceptable levels of microbial contamination in CRRTs, a potential for clinically significant transfer of pyrogens to highly vulnerable, critically ill patient populations. A regular surveillance of circuit set-up and maintenance is fundamental to prevent this complication.

Anticoagulation

The contact of blood with the extracorporal circuit, lines, and membrane activates platelets and the production of a variety of inflammatory and prothrombotic mediators. The result is the induction of fibrin deposition and filter clotting. Clotting of the dialyzer reduces its longevity, and more importantly, reduces the efficiency of solute clearance. Inefficient anticoagulation reduces the dialyzer performance by diminishing the surface of the membrane available for diffusion or convection. The mainstay of anticoagulation for IHD is unfractionated heparin. Heparin is usually administrated as a bolus, followed by a continuous infusion into the arterial line. The optimal dose for AKI patients is not established. The target is to maintain a partial thromboplastin time of 1.5 to 2 times the normal level. Low molecular weight heparin is excreted mainly by the kidneys, thus monitoring of factor Xa levels is necessary in patients with impaired kidney function.

In patients at high risk of bleeding, systemic anticoagulation should be avoided. IHD is often performed without anticoagulation. The high blood flow and the short duration of treatment prevent the filter from clotting, especially in patients with thrombocytopenia or coagulopathy, or both. The use of intermittent saline flushes every 15 to 30 minutes in the arterial line of the circuit helps to wash fibrin strands from the membrane. The volume administered on the flushes must be included in the net ultrafiltration.

An alternative to systemic anticoagulation is regional anticoagulation. Regional anticoagulation with citrate is being more frequently used in continuous and intermittent methods. Citrate is infused continuously in the arterial line and chelates the free calcium in the circuit, inhibiting the coagulation cascade. Part of the complex, calcium-citrate, is removed by dialysis clearance and part is metabolized in the liver. The infusion of citrate is adjusted to keep the activated clotting time longer than 160 seconds. Serum calcium concentrations (preferably ionized) should be monitored and continuous or intermittent calcium infusion performed as necessary. The use of regional citrate anticoagulation (RCA) increases the buffer load during the treatment as citrate is converted to bicarbonate in the liver. The possibility of metabolic alkalosis requires modifications in the hemofiltration solution or dialysate. One trial compared the hemofilter survival time to RCA compared to heparin. In the RCA group, the lifetime of hemofilter was significantly longer: 124.5 hours versus 38.3 hours in the heparin group ($P < 0.001$).[98] In a recent single-center study, Oudemans-van Straaten and coworkers[99] randomized 215 patients, comparing RCA with low molecular weight heparin (nadroparin) in CVVH. Although the circuit survival was not significantly different between groups and the study was not powered to detect a difference in survival, the RCA group mortality was significantly lower (45% vs. 62% nadroparin, $P = 0.02$). The RCA survival benefit could not be explained by difference in dose of CVVH, incidence of bleeding, transfusion, or metabolic alkalosis. The authors have speculated that RCA could have resulted in lower mortality by blocking inflammation, based on previous studies in chronic dialysis patients.[100,101] These previous studies have demonstrated that dialysis-induced polymorphonuclear cell degranulation is primarily ionized calcium (iCa)-dependent and is abolished during RCA dialysis. A more recent study by Gabutti and associates[102] demonstrated a favorable effect on interleukin-1ß release associated with RCA dialysis. The potential beneficial effects of RCA on survival and its underlying mechanism are subjects for future studies. In spite of previous concerns about RCA, several studies have proven its safety and effectiveness.

To prevent central venous catheter thrombosis during the interdialytic period, heparin and saline are commonly used to fill the lumen. When using heparin as a filling solution, any excess amount causes systemic heparinization, and gastrointestinal and puncture-site bleeding after heparin-free dialysis has been associated with heparin used as lock solution.

Trisodium citrate has been advocated as a lock solution because it is free of side effects in the amount used for catheter filling safer and its antimicrobial properties. In a multicenter, double-blind, randomized, controlled trial in ESRD patients,[103] 30% trisodium citrate was compared to unfractionated heparin 5000 units/ml for prevention of catheter-related infections, thrombosis, and bleeding complications. Catheter removal for all complications was 46% in the heparin group, compared to 28% in the trisodium citrate group ($P = 0.005$). Catheter related bacteremia rates were 1.1/1000 catheter-days in the trisodium group versus 4.1 in the heparin group ($P < 0.001$), and the study was stopped prematurely because of this difference. Thus in patients at high risk of bleeding or infection, the use of citrate concentrated solutions can contribute to reduce premature removal and catheter-related infections.

Dose of Dialysis

The ideal dialysis prescription for AKI should incorporate an assessment of the dose of dialysis delivered. Unfortunately, there are no standard methods for assessing the dose of dialysis in AKI. In ESRD, the dose of dialysis prescribed and delivered is usually based on an assessment of the amount of urea removed, using urea kinetic modeling either via direct dialysis quantification or using regression formulas incorporating fractional urea reduction.[104–106] A key feature of these methods is the assumption that patients with ESRD are in steady state with respect to urea generation, volume status, and renal and extrarenal clearance. However, dialysis dosing in AKI needs to account for highly variable body water volumes and varying urea generation rates, and different methods of dialysis and changes in renal and extrarenal clearance. Unfortunately, these issues have not been accurately quantified or adequately studied in prospective cohort studies or clinical trials conducted to date.

In general, the dose of dialysis is based on modality-specific criteria (e.g., membrane choice, operational characteristics, and the duration of each dialysis session). For patients treated with IHD, the frequency of dialysis is another determinant of the overall dose of dialysis delivered. Table 50-3 shows a comparison of the factors affecting dose of dialysis for IHD and CRRT. Several investigators have attempted to quantify the dose of dialysis delivered in AKI using methods used for patients with ESRD. Clark and colleagues[107] compared IHD to CRRT techniques using a computer model to derive the required IHD frequency (per week) or required CRRT for a given patient weight for desired BUN values of 60, 80, and 100 mg/dl. For the attainment of intensive IHD metabolic control (BUN = 60 mg/dl) at steady state, a required treatment frequency of 4.4 dialyses per week was predicted for a 50-kg patient. However, the model predicted that the same degree of metabolic control could not be achieved even with daily IHD therapy in patients weighing 90 kg or more. On the other hand, for the attainment of intensive CRRT metabolic control (BUN = 60 mg/dl), required urea clearance rates of approximately 900 ml/hr and 1900 ml/hr were predicted for 50- and 100-kg patients, respectively. These data suggest that, for many patients, rigorous control of azotemia equivalent to that readily attainable with most CRRT programs can be achieved with intensive (nearly daily) IHD regimens only. In practice, the frequency of dialysis usually depends on the patient's clinical and biochemical status. It is noteworthy that reimbursement policies in the United States currently do not support the practice of daily IHD.

The role of aggressive dialysis on outcome from AKI has been addressed in previous studies.[37,108] Schiffl and colleagues[109] conducted a randomized clinical trial comparing conventional alternate day dialysis to daily dialysis among 160 patients with AKI, assessing 14-day survival. The groups were similar with respect to baseline characteristics and illness severity and were analyzed by intention to treat. In the daily group, the weekly delivered Kt/V was 5.8 plus or minus 0.4, and in the conventional group it was 3 plus or minus 0.6. The duration of therapy was 3.3 hours per session in the daily group and 3.4 hours per session in the conventional group. The daily HD group had improved survival (28% vs. 46%, $P = 0.01$) and recovered kidney function more quickly (9 ± 2 days vs. 16 ± 6 days, $P = 0.001$). Factors significantly associated with an increased odds of death included alternate day HD (vs. DHD) (OR, 3.92; 95% CI, 1.68 to 9.18; $P = 0.002$), higher APACHE III scores (OR, 1.06; 95% CI, 1.01 to 1.12 per point increase; $P = 0.02$), oliguria (OR, 3.02; 95% CI, 1.35 to 6.77; $P = 0.007$), and sepsis (OR, 3.27; 95% CI, 1.43 to 7.5; $P = 0.005$).[109] The Schiffl study was the first randomized trial suggesting that patients with AKI benefited from more frequent HD and, consequently, a higher weekly Kt/V.[109]

Ronco and colleagues[110] performed a randomized controlled trial with 425 subjects receiving three different doses of postdilution CVVH: 20, 35, and 45 ml/kg/hr. Subjects receiving doses of 45 and 35 ml/kg/hr experienced lower mortality rates compared to subjects receiving 20 ml/kg/hr, 42% and 43% versus 59%, respectively ($P < 0.005$). After this study was published, three other randomized clinical trials (RCTs) showed contradictory results. Bouman and colleagues[43] found no difference in mortality among subjects who received higher hemofiltration volumes 48.2 ml/kg/hr versus 19.5 ml/kg/hr. Tolwani and colleagues[111] randomized 200 patients for CVVHDF using two different ultrafiltration volumes. The intensive group received 29 ml/kg/hr against 17 ml/kg/hr for those in standard group. There was no significant difference in the mortality rate between groups: 64% verus 60% ($P = 0.56$). Adding a diffusive component (18 ml/kg/hr of dialysate) in 206 patients submitted to hemofiltration (25 ml/kg/hr of replacement fluid), Saudan and colleagues[112] showed a significant decrease in mortality 46% versus 61% ($P = 0.0005$). In this study, subjects in the hemodiafiltration group received substantially more overall solute clearance than subjects in the hemofiltration group, making it difficult to determine if the reduction in mortality was attributable to the higher dose or the addition of diffusive clearance.

The largest study to date on dose of dialysis is the VA/NIH Acute Renal Failure Trial Network (ATN) Study, which has led nephrologists and intensivists to question the benefit of higher dialysis dose. The ATN trial was a randomized multicenter study including 1124 critically ill AKI patients with sepsis or at least one nonrenal organ dysfunction aimed at providing a definitive conclusion on the benefits of intensive versus less-intensive dialysis dosage.[17] Intensive dosage was defined as CRRT with an effluent rate of 35 ml/kg/hr, IHD or SLED six times per week and

less-intensive dosage, as CRRT with an effluent rate of 20 ml/kg/hr, and IHD or SLED three times per week. Each IHD or SLED treatment was aimed at achieving a single-pool Kt/V_{urea} of 1.2 to 1.4. The mean delivered dosages (5.4 treatments per week vs. 3 treatments per week at Kt/V of 1.3 or effluent rate of 35.8 vs. 22 ml/kg/hr) were almost identical to the prescribed dosages. Subjects were switched from one modality to another according to their Sequential Organ Failure Assessment (SOFA) cardiovascular score (IHD when the score was 0 to 2 and CRRT or SLED when the score was 3 or 4). Baseline characteristics were similar between the groups. There were no differences in the primary endpoint, mortality at 60 days, or in the duration of renal replacement therapy, rate of recovery of kidney function, or nonrenal organ failure between the groups. In contrast to the Bouman and Tolwani studies,[43,111] the sample size of the ATN study was large enough that there was adequate power to detect modest differences in mortality.

The design of the ATN study did not include predetermined strategies for some parameters that may have influenced the results, such as the timing of initiation of therapy, fluid balance, and site of delivery of replacement fluids (pre- vs. postdilution). It is important to note that subjects in the less intensive group received more renal replacement therapy than most patients in routine clinical practice. Therefore, practitioners should not conclude that dose is unimportant. In AKI there is a marked discrepancy between prescribed and delivered dose of dialysis. The delivered Kt/V in patients AKI have been shown to be 30% lower than prescribed,[109,113] resulting from hypotension, dialyzer clotting, and vascular access recirculation.[114]

Other promising concepts should also be prospectively tested to improve our current understanding of the pathophysiology of acute kidney injury and to help better define dialysis dosage requirements. To improve the definition of dialysis dosage, other dialysis parameters, such as fluid balance, need to be assessed. In CRRT the effluent volume per se may not accurately reflect clearance, because clotting of filter is associated with declining efficacy in effluent saturation. Although current RRTs substitute small solute and volume clearances, the later parameter has never been included in randomized studies on dialysis dosage in AKI.[17,43,55,109–112] More importantly, fluid excess has been shown to be independently associated with increased mortality in one adult and several pediatric observational studies in AKI.[55,115–118] Fluid excess was usually defined as a proportion of initial hospital admission weight. In the largest pediatric study, the percentage fluid excess at dialysis initiation was significantly lower in survivors versus nonsurvivors ($14.2 \pm 15.9\%$ vs. $25.4 \pm 32.9\%$; $P < 0.03$), even after adjustment for severity of illness.[115] Therefore, fluid excess may contribute to imbalances between groups and should be better characterized in future studies. Results from the ongoing RENAL trial, a multicenter trial comparing augmented versus normal CRRT regimen, may add additional insight into the question of dialysis dose and outcome.

Intermittent Versus Continuous Therapy

The choice of intermittent or continuous therapy is currently largely based on the availability of CRRT and the familiarity of the nephrologist and other personnel, particularly ICU staff, with the procedure. In centers where CRRT is routinely done, this choice is usually based on the experience of the nephrologist. It is helpful to compare the operating characteristics of the two therapies to recognize the strengths and weaknesses of each modality (see Table 50-4). Although difficult, comparisons of solute control, fluid balance, nutritional support, and outcome are relevant for the choice of modality and are discussed briefly in the following text.

Fluid removal is a desirable component of any renal replacement therapy and is a major goal of renal replacement for AKI.[119] Fluid removal, and hence fluid balance, is limited to the period of dialysis. If the patient is hemodynamically unstable during this period, it may be difficult to remove any fluid. Fluid removal is slower and hypotension is uncommon with PD and continuous hemofiltration. It has been suggested that the latter modality may be associated with an improved outcome, perhaps because of more stable hemodynamics;[120] however, this has not been rigorously demonstrated.[47] The high efficacy of these therapies in continuous fluid removal lends them for use in situations other than renal failure, such as heart failure.[121,122] Pediatric patients are better suited for PD and CRRT, and these modalities have been used successfully in the management of AKI in neonates.[118,123–125]

Continuous therapies have an advantage over IHD in permitting the provision of optimal nutrition because fluid removal is not a limiting factor of therapy. In the overall nutritional balance of the patient, two other factors need to be recognized: the composition of the dialysate and composition of hemofiltrate or replacement fluid. First, lactate-based dialysis and hemofiltration solutions can rarely result in hyperlactatemia and worsening of acid-base status. Additionally, when lactate-buffered substitution fluids are used in CRRT, it can cause higher urea generation rates, as compared to bicarbonate solutions.[126,127] Second, glucose containing dialysate solutions result in glucose absorption during the dialysis procedure, which contributes to the caloric load. This glucose content is also associated with an increase in endogenous insulin secretion in most patients, and some patients may require exogenous insulin.[128] Avoidance of peritoneal dialysate and the use of a lower dextrose concentration-based dialysate in CRRT usually prevent this complication. A second nutritional factor is the dialysance of amino acids, vitamins, and trace elements across the filter. Losses appear to depend more on the serum levels than on the underlying clinical status of the patient.[129–132] To avoid potential harm, vitamin supplementation should be provided for all patients on CRRT regardless of dialysis dose and pharmacists should be consulted to optimize drug dose adjustments.[133] With the massive expansion of therapeutic alternatives in critical care (especially antibiotics), much more research is required to understand optimal dose delivery in response to CRRT.

A major question, still unanswered, relates effect of the dialysis modality on outcome. Two issues are pertinent: the outcomes of interest and the causal link of choice of modality to the outcome. Both IHD and PD were the major therapies until a decade ago. In four prospective cohort studies,[84,134–136] none suggest differences in mortality between modalities. A recent systematic review[137] identified nine RCTs that compared CRRT versus intermittent methods.[138–146] The relative risk of death associated with CRRT was not significantly different from that seen with IHD (RR, 1.10; 95% CI, 0.99 to 1.23) (Table 50-6). The

TABLE 50-6 Randomized Clinical Trials Evaluating Dialysis Dose in Acute Kidney Injury over the Past Decade

AUTHOR, YEAR (REFERENCE)	NUMBER OF PATIENTS	STUDY DESIGN	DIALYSIS INITIATION: MEAN TIME AFTER BUN (mg/dl)	DIALYSIS INITIATION: MEAN TIME AFTER ICU ADMISSION	DIALYSIS MODALITY	ASSESSMENT OF DOSE	INTENSIVE GROUP DELIVERED DOSE	CONTROL GROUP DELIVERED DOSE	MORTALITY INTENSIVE vs. CONTROL (%)	DIFFERENCE IN MORTALITY
Ronco, 2000[110]	425	Single-center RCT	51	NA	CVVH—postdilution	Ultrafiltration volume in ml/kg/hr	35 and 45 ml/kg/hr[#]	20 ml/kg/hr[#]	42 and 43 vs. 59[*]	$P < 0.005$
Schiffl, 2002[109]	160	Single-center RCT	89	NA	IHD	Frequency (3/week vs. daily)	Weekly delivered Kt/V 5.8 (by session-0.94)	Weekly delivered Kt/V 3 (by session-0.92)	28 vs. 46	Odds ratio, 3.92; 95% CI, 1.68 to 9.18; $P = 0.01$
Bouman, 2002[43]	106	RCT in two centers	46 vs. 105[δ]	6.5 vs. 41.8 hr[δ]	CVVH (HVHF early initiation, LVHF early and late initiation)	Ultrafiltration volume ml/kg/hr	48.2 ml/kg/hr	19.5 ml/kg/hr	37 vs. 46[***]	0.58
Saudan, 2006[112]	206	Single-center	88	NA	CVVH vs. CVVHDF—predilution	Ultrafiltration volume ml/kg/hr	CVVHDF (24 ml/kg/hr replacement fluid + 18 ml/kg/hr dialysate)	CVVH (25 ml/kg/hr replacement fluid)	46 vs. 61[**]	$P = 0.0005$
Tolwani, 2008[111]	200	RCT	75	8 days	CVVHDF—predilution	Ultrafiltration volume ml/kg/hr	29 ml/kg/hr	17 ml/kg/hr	64 vs. 60[***]	= 0.56
Palevsky, 2008[17]	1124	Multicenter RCT	66	6-7 days	IHD, SLED, and CRRT	Ultrafiltration volume ml/kg/hr Frequency and duration of session	IHD 5.4/week SLED 6.2/week (session Kt/V1.3) CRRT 35.8 ml/kg/hr	IHD 3/week SLED 2.9/week (session Kt/V 1.3) CRRT 22 ml/kg/hr	53.6 vs. 51.5	Odds ratio, 1.09; 95% CI, 0.86 to 1.40; $P = 0.47$
Bellomo, ongoing		Multicenter RCT			CVVHDF	Ultrafiltration volume ml/kg/hr	40 mL/kg/hr[#]	25 ml/kg/hr[#]		

Blood urea nitrogen in mg/dl may be converted to mmol/L by multiplying by 0.357.
BUN, blood urea nitrogen; *CI,* confidence interval; *CRRT,* continuous renal replacement therapy; *CVVH,* continuos veno venous hemofiltration; *CVVHDF,* continuous veno venous hemodiafiltration; *HVHF,* high volume hemofiltration; *HVPD,* high volume peritoneal dialysis; *ICU,* intensive care unit; *IHD,* intermittent hemodialysis; *LHVF,* low volume hemofiltration; *NA,* not available; *RCT,* randomized clinical trial; *RRT,* renal replacement therapy; *SLED,* sustained low efficiency dialysis.
[*]Mortality assessment was done 15 days after interruption of RRT.
[**]3 months mortality.
[***]Hospital mortality.
[#]Prescribed.
[δ]Early vs. late groups.

last Cochrane review comparing dialysis modalities concluded that in hemodynamically stable patients, modality does not appear to influence outcomes. In hemodynamically unstable patients, CRRT may be preferable, because patients on CRRT maintain higher mean arterial pressure and show a trend towards lesser need for escalation of vasopressor therapy and arrhythmias.[147]

It is now apparent that more than one therapy is used for managing patients with AKI. As shown in Table 50-5, transitions in therapy are common and reflect the changing needs of patients during their hospital course. For instance, patients in the ICU may initially start on CRRT when they are hemodynamically unstable, transition to SLED-EDD when they improve, and leave the ICU on IHD. In the recent ATN trial 57% of the patients had more than one therapy while 23% and 20% had IHD and CRRT alone.[17] We recommend that all therapies should be used as indicated to best support patient needs through their course.

Other Factors

Procedure-Related Complications

The most common complication in RRT is hypotension, occurring in 30% to 50% of patients.[17,148] Improvements in hemodialysis techniques have reduced the hemodynamic challenges of traditional IHD. Ultrafiltration control and variable sodium modeling are frequently used techniques to avoid episodes of hypotension in AKI patients. Paganini and colleagues[149] showed an improved hemodynamic stability using sodium modeling (160 mEq/L to 140 mEq/L over the course of dialysis) and ultrafiltration profiling (50% ultrafiltration in the first hour and 50% over the remainder of the dialysis session) compared to fixed parameters. In CRRT the prolonged time can increase the risk of volume depletion, and hemostatic and metabolic alterations (Table 50-7).[17,137] Although these techniques have been demonstrated as efficient in diminishing the episodes of hypotension, the impact on AKI patients is not known. In spite of the expected safety of obtaining fluid removal over a longer period of time with CRRT, careful monitored is mandatory. Recent reports of technical problems in CRRT related to machine malfunction, medication errors, and compounding errors, showed an association with increased patient morbidity and mortality.[150]

An important concern is that episodes of hypotension during dialysis could adversely influence renal outcome.[151] The development of oliguria following initiation of dialysis is fairly common and may be more frequent with IHD in comparison to CRRT or PD.[152] Nevertheless, no difference in dialysis-independence rates was found between modalities in five different randomized trials[138–141,143] and two metaanalyses.[147,153] Only one randomized study, performed with IHD, has found a faster renal recovery in patients assigned to daily dialysis compared to every other day dialysis treatments (9 ± 2 days vs. 16 ± 6 days; $P = 0.001$).[109] Recently, the ATN trial, using both continuous and intermittent dialysis, found no difference in renal recovery by multiple definitions between more intensive and less intensive dialysis groups.[17]

Patients with hepatic encephalopathy, underlying neurological and preexisting hyponatremia disorders, may be at increased risk for dialysis disequilibrium syndrome. This syndrome occurs when rapid urea removal is achieved, with IHD resulting in brain edema.[154,155] It is more commonly seen in ESRD but can also complicate AKI.[154–156] Recently, the recognition of different profiles of urea transporters in the brain of chronic uremic rats has elucidated the mechanisms underlying this syndrome.[157] Reduced intensity of dialysis sessions or the prescription of SLED/EDD affords more gradual removal of urea and time for osmotic gradient adjustment in the brain.

Hypoxemia during hemodialysis had been frequently described during dialysis. Besides other possible causes of hypoxemia associated with inflammatory response and respiratory alkalosis, either by use of CO_2 in the conversion to bicarbonate or by diffusion from high bicarbonate dialysate, induces hypoventilation and contributes to worsen hypoxia.[158,159] This effect is more pronounced in patients with underlying lung disease and those with chronic obstructive pulmonary disorder during or after hemodialysis.

Because CRRT requires anticoagulation for a longer period of time, the risk for complications related to anticoagulation may be higher. In EDD, moderate blood flow rates and anticoagulation requirements may limit hypotension relative to IHD and bleeding complications relative to CRRT.[21]

TABLE 50-7 Selected Major Complications of Intermittent Hemodialysis and Methods of Prevention

COMPLICATION	PREVENTIVE MEASURE(S)
Hypotension	Extend dialysis time
	Perform sequential ultrafiltration hemodialysis
	Discontinue antihypertensive (not antianginal) agents
	Decrease dialysate temperature
	Increase dialysate calcium concentration
	Increase hemoglobin concentration
	Consider administration of colloid
	Consider change in estimated dry weight
Arrhythmia	Increase dialysate potassium concentration
	Consider discontinuing digoxin and other antiarrhythmic agents
	Supplemental oxygen during dialysis
Muscle cramps	Extend dialysis time
	Consider hypertonic saline
	Consider vitamin E
	Consider quinine sulfate
Pyrogen reaction	Culture dialysate
	Immediate water testing for LPS
Dialysis disequilibrium	Attenuate clearance by limiting time, dialyzer surface area, blood flow, and dialysate flow consider mannitol
Hypoxemia	Use noncellulosic dialyzer
	Supplemental oxygen during dialysis
Hemolysis	Examine blood lines
	Immediate water testing for chloramines

Cost

The cost of RRT for patients with AKI is high; however, information on the costs of the three dialytic techniques for AKI is minimal. For IHD, major costs include the need for supervision by a trained dialysis nurse, which can become

an economic issue if IHD is performed on a frequent or daily basis. For CRRT major costs include disposables and replacement fluids. Most investigators have found that CRRT costs are somewhat greater than IHD.[153,160] An evaluation of total hospital costs[161] showed that from the start of RRT to hospital discharge, the total cost for patients on CRRT was $57,000 more than costs for those on IHD. A recent cost analysis of the of RRT for patients with AKI estimated that mean adjusted total costs were $1342/week for IHD compared to $3486/week for CRRT,[160] and no difference was found in the outcome and renal recovery at hospital discharge. However, there was a trend toward enhanced renal recovery in the CRRT group despite a significantly lower mean arterial pressure and a trend toward higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Considering that nonrecovery of renal function would adversely affect quality of life, a modality that enhanced the rate of renal recovery would offer an important advantage, even if there were no difference in survival across modalities.

Future trials for dialysis in AKI need to standardize approaches for timing of initiation, dose, modality, care delivered, and ascertain the health economic consequences among outcomes.

Nursing Expertise and Other Support

IHD, CRRT, and APD are renal nursing procedures; however, CRRT and APD require a significant effort by ICU nurses in addition to nephrology nursing support.[162,163] It is impossible to institute CRRT without an adequate in-service training of ICU nurses and their active participation in the procedure. This is usually facilitated by the availability of flow sheets, manuals (for pumped circuits) and backup attending physician support. Additionally, since CRRT requires changes in drug dosing, nutrition and pharmacy personnel should be actively involved. If CRRT is performed infrequently, there is a greater chance of problems and the continued need for frequent in-service training of dialysis and ICU personnel to maintain skills.[162]

Recommendations for Initial Choice of Renal Replacement

Despite the lack of definitive results derived from randomized clinical trials, it is possible to develop a rational approach to the selection of a dialysis modality for the initial treatment of AKI in critically ill patients. A primary consideration is the availability of a technique at the center and familiarity and comfort of personnel with the technique. The latter point is extremely important with respect to continuous techniques as infrequent use may be associated with a higher incidence of iatrogenic complications.[164,165] Other considerations are the complexity of the patient, the location in the hospital, and need for mobility.

Patients with uncomplicated AKI can be treated with IHD or PD, and the choice is based on other patient characteristics (e.g., pregnancy, hemodynamic tolerance, access, and urgency for treatment). Patients with MOF and AKI can be treated with CRRT or IHD. In general, hemodynamically unstable, catabolic, and excessively fluid overloaded patients are treated with CRRT, whereas IHD may be better suited for patients requiring early mobilization and who are more stable.[137] Table 50-8 depicts a potential therapy for several different clinical scenarios. Among continuous therapies, those that include hemofiltration (CVVH, CVVHDF) may be superior in sepsis or the systemic inflammatory response syndrome because of the ability to more efficiently remove (or adsorb) larger molecular weight solutes.[121,166] For most clinical scenarios, we favor the use of hemodiafiltration techniques that combine hemodialysis and hemofiltration, thus providing optimal clearance for both small and large molecules. It is important to stress that one of the key factors in the choice of renal replacement is to tailor the therapy to the patient. This implies an ongoing assessment of the patient and modification of the therapy used based on clinical criteria (e.g., in a hemodynamically unstable patient CRRT may be an initial choice; however, when the patient is more stable and needs to be mobilized, IHD may be more appropriate). We suggest that flexibility in using the entire range of renal replacement therapies is an important overall philosophy in the management of AKI.

TABLE 50-8 Renal Replacement Therapy for Acute Kidney Injury: Initial Choice

INDICATION	CLINICAL SETTING	MODALITY
Uncomplicated AKI	Antibiotic nephrotoxicity	IHD, PD
Fluid removal	Cardiogenic shock, CP bypass	SCUF, CVVH, CVVHD, SLED
Uremia	Complicated AKI in ICU	CRRT (CVVHD, CVVH, CVVHDF), IHD, SLED
Increased intracranial pressure	Subarachnoid hemorrhage, hepatorenal syndrome	CRRT (CVVH, CVVHDF), SLED
Shock	Sepsis, ARDS	CRRT (CVVH, CVVHDF)
Nutrition	Burns	CRRT (CVVHD, CVVHDF, CVVH), SLED
Poisons	Theophylline, barbiturates	IHD, SLED, CVVHD
Electrolyte abnormalities	Marked hyperkalemia	IHD, SLED, CVVHD

AKI, acute kidney injury; *ARDS,* acute respiratory distress syndrome; *CP,* cardiopulmonary; *CRRT,* continuous renal replacement therapy; *CVVH,* continuous veno venous hemofiltration; *CVVHD,* continuous veno venous hemodialysis; *CVVHDF,* continuous veno venous hemodiafiltration; *ICU,* intensive care unit; *IHD,* intermittent hemodialysis; *PD,* peritoneal dialysis; *SCUF,* slow continuous ultrafiltration; *SLED,* sustained low efficiency dialysis.

SUMMARY

Several new methods of dialysis are now available to treat AKI. Rational use of these techniques requires an understanding of factors influencing the choice of a modality and appreciation of the advantages and disadvantages of each technique. Management of AKI is different from that of ESRD, and the dialysis prescription should incorporate the unique characteristics of each patient. Therapeutic alternatives to traditional IHD now permit nephrologists to match the modality to the patient. This approach and additional research will allow better management of patients with AKI and ultimately improve survival and other important outcomes.

A full list of references are available at www.expertconsult.com.

Chapter 51

EXTRACORPOREAL TREATMENT OF POISONINGS

Stuart Abramson, M.D., M.P.H

The 2006 Annual Report of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) recorded 2,403,539 human exposure cases reported by 62 poison centers during 2006.[1] That was an increase of 12% compared to 1995, and an increase of 118% as compared to 1986.[2] A total of 299.4 million people were served by the participating centers, with an average of eight exposures per 1000 people. Of the exposures, 91% were acute and 92% involved a single poison. Sixty percent of the exposures were unintentional, while suicidal intent comprised 8% and intentional misuse comprised 2% of the exposures.[1]

About 27% of recognizably poisoned patients are treated in a healthcare facility, and 7% require admission to the hospital.[1] Less than 0.1% of all exposed patients die. The mortality rate is higher for intentional exposures, where 0.3% die, and these patients comprise 78% of all fatalities in exposure cases.[1] Three percent of the recognizably poisoned patients require intensive medical care, including hemodynamic and ventilatory support with close monitoring in a special care unit. The remainder recovers with general support and ward nursing supervision. Fewer than 5% of cases of recognizable poisoning are amenable to techniques that facilitate the elimination of the poison.[1]

A number of exposures still carries a high morbidity and mortality secondary to the toxic effect of the poison or its metabolic byproducts.[3] Lithium, for example, causes its toxic effect directly.[4] On the other hand, the two most toxic alcohols, ethylene glycol and methanol, are converted to glycolate and formate, respectively. These metabolites cause the metabolic abnormalities and end organ damage seen with ingestion of ethylene glycol or methanol.[5] Many of the toxic effects of poisonings, such as hypotension, acidosis, seizures and decreased mentation, are reversible.[6] Less commonly, the toxic effect can be permanent, such as the neurological effects of methanol or lithium, renal failure from ethylene glycol or, rarely, subsequent death from the complications of any of the intoxications discussed in this chapter.[7]

This chapter reviews the strategies to limit the toxic effects of various poisonings. It will start with the initial approach to the intoxicated patient, which includes techniques to limit further absorption, antidotes to specific toxins, strategies to enhance endogenous elimination, and evaluation to determine the nature and severity of the intoxication. General considerations to help with decisions regarding extracorporeal therapy initiation and prescription will then be detailed. A brief review of the types of therapies available to the nephrologist including hemodialysis, hemoperfusion, and continuous modalities will follow. Finally, this chapter will discuss in detail the intoxicants that are most effectively removed by these therapies.

APPROACH TO THE POISONED PATIENT

After supplying supportive measures to maintain airway, breathing and circulation, the "ABCs," the management for a poisoned patient should be directed toward decreasing or limiting toxin accumulation.[3]

Prevention of Further Absorption

The first therapeutic intervention should be directed at preventing further absorption of the compound in question. The four methods of GI tract decontamination are emesis, gastric emptying, whole-bowel irrigation, and adsorption using an oral sorbent with catharsis.[8] Ipecac-induced emesis is rarely beneficial in toxic exposures for patients treated in the hospital.[9] Gastric lavage has limited use in the management of the poisoned patient; it has been associated with an increased risk of aspiration, arrhythmia, and stomach perforation, and no clinical studies have shown an improvement in outcome with the use of gastric lavage.[10]

Whole bowel irrigation with a solution of electrolytes and polyethylene glycol may be beneficial in the elimination of undissolved tablets or pills.[8] It is most likely to be beneficial in the management of intoxication with sustained release or enteric-coated drugs or in toxins that are poorly adsorbed by activated charcoal, such as arsenic and lithium.[11] The optimal regimen has not been well-established, but most of the studies used 1 to 2 L/hr for 3 to 5 hours.[12,13] It is time consuming and is contraindicated in patients with an ileus, hemodynamic instability, or a compromised airway.[14]

Oral sorbents (primarily activated charcoal) can bind unabsorbed drug in the gastrointestinal (GI) tract and therefore promote its elimination by decreasing its absorption.[15] Activated charcoal is most helpful in the elimination of salicylates, phenobarbital, and theophylline.[16] It is administered as an aqueous suspension with a minimum of 8 ml of water to each gram of powder.[15] Commercial premixed formulations are available that may contain activated charcoal with a lubricant (e.g., propylene glycol or carboxymethylcellulose) or a cathartic (e.g., sorbitol). The mean transit time of activated charcoal in fasting subjects is 25 hours; this can be reduced to 1.1 hours with sorbitol.[17] There are a number of associated risks with the use of cathartics, including hypotension, dehydration, and hyperglycemia.[18] The administration of a cathartic alone has no role in the management of the poisoned patient.[18] The American Academy of Clinical Toxicology (AACT) recommends limiting cathartic use to a single dose to lower the risk of adverse effects.[18]

Activated charcoal can be administered orally or via a nasogastric tube. The recommended dose is 10 times the weight of the ingested chemical or as much as possible if the dose of poison is unknown, up to 1 g/kg patient weight. Single-dose activated charcoal has been shown to be most effective if given within 1 hour of ingestion.[15] Its use may be considered after 1 hour in ingestions where delayed GI absorption is more likely (e.g., sustained release and enteric-coated preparations).[19] It should be used only in patients with an intact or protected airway.[15]

Enhancing Endogenous Elimination

The second step in minimizing toxin accumulation or promoting its removal is to facilitate endogenous excretion through forced diuresis, manipulation of urinary pH, or removal of toxin via the gut.[19]

Forced Diuresis

Forced diuresis is a technique using volume loading to decrease tubular reabsorption.[20] The goal is to achieve urine flow rates of 6 cc/kg/hr with the combination of isotonic fluids and diuretics.[21] It has the potential to cause significant volume and electrolyte imbalance and has not been shown to be effective in enhancing toxin elimination.[22] Forced diuresis is therefore not recommended as a technique to enhance endogenous elimination in the poisoned patient.

Urinary pH Manipulation

Urinary pH manipulation can effectively decrease tubular reabsorption of weak nonpolar acids and bases. Manipulation of the urine pH can enhance the excretion of acidic or basic chemicals through a mechanism known as ion trapping.[23] The membranes of the nephron are generally more permeable to nonionized and nonpolar molecules. Compounds are filtered and secreted in the nonionized form of weak acids or bases by nonionic diffusion across cell membranes. With manipulation of urinary pH, the change in the intraluminal pH promotes the formation of a higher intratubular fraction of the ionized drug, effectively trapping the ionized moiety in the urinary space since the ionized form can no longer cross the cell membrane.[23] For weak acids, alkaline urine increases the fraction that is ionized. Acidic urine does the same for weak bases. In each case, an increase in the ionized form of the drug decreases reabsorption, enhancing renal elimination.[24] Urine alkalinization can be used to enhance the elimination of salicylates and phenobarbital.[25] There is also some evidence for its efficacy in methotrexate toxicity and poisoning with the chlorophenoxy herbicides.[23] Urinary acidification can be used to enhance the elimination of chloroquine, amphetamine, quinine, and phencyclidine.[26]

Alkalinization of the urine can be achieved by adding 150 mEq sodium bicarbonate to 1 L of dextrose 5% in water (D5W) to run at 100 to 250 cc/hr. The goal is to achieve a urinary pH of greater than 7, which usually requires 0.25 to 0.5 mEq/kg/hr (Table 51-1).[27] This can only be achieved if the patient has intact renal function, and urinary alkalinization should be avoided in patients with severe acute kidney injury (AKI). Risks of urinary alkalinization include volume overload, alkalemia, hypernatremia, and hypokalemia.[23] It is important to treat the hypokalemia, because it will prevent the alkalinization of the urine by promoting distal hydrogen secretion in place of potassium secretion. Hypokalemia can be avoided by adding 20 to 40 mEq potassium chloride to each liter of D5W with sodium bicarbonate.[19] Acetazolamide will enhance urinary alkalinization but should be avoided because of the risk of worsening systemic acidemia,

TABLE 51-1 Urine Alkalinization

Sodium bicarbonate 150 mEq in 1 L D5W (dextrose 5% in water)
Fluid to run at 100-250 cc/hr
Aim for 1-2 mEq/kg every 3-4 hours to achieve urine pH = 7.5-8.5
Treat hypokalemia by adding 20-40 mEq KCl per L
Avoid in patients with acute or chronic kidney disease

(From A.T. Proudfoot, E.P. Krenzelok, J.A. Vale, Position paper on urine alkalinization, J. Toxicol. Clin. Toxicol. 42 [1] [2004] 1–26.)

which can enhance toxicity of certain poisonings, most notably salicylates.[28]

Urinary acidification is rarely used because of the potential to worsen renal injury in many poisonings. Arginine hydrochloride or ammonium chloride have been shown to be effective urinary acidification agents. Although urinary acidification may enhance elimination of weak bases, it cannot be recommended as a treatment for toxicity from these compounds. Complications of urinary acidification include myoglobinuria, acute renal failure, and hyperkalemia.[26]

Multidose Activated Charcoal

A few drugs undergo enterohepatic or enteroenteric circulation. Multidose activated charcoal (MDAC) can enhance elimination of these drugs by interrupting this circulation. Drugs that will have enhanced elimination with MDAC include carbamazepine, dapsone, phenobarbital, quinine, and theophylline.[29] There have not been any studies, however, that show that MDAC improves mortality or morbidity from toxicity due to these drugs.[30] The AACT recommends that its use be considered only in patients who have ingested a potentially lethal amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. The standard regimen is to administer activated charcoal 1 g/kg and then 0.5 g/kg at 2- to 6-hour intervals.[30]

ANTIDOTES

The third strategy is to convey protection against the toxin by administering specific antidotes, antibodies, or substrate inhibitors. Antidotes and antibodies are available for a limited number of poisonings (Table 51-2). The timing of their administration can be crucial, and most antidotes are only adjunctive therapy to aggressive supportive care. The antidotes ethanol and fomepizole can be used for the toxins methanol and ethylene glycol and will be discussed below.[5] There are a number toxins where administration of the antidote is the primary therapy, and there therapy are well-reviewed elsewhere.[6]

TABLE 51-2 Drugs and Poisons Treated With Specific Antidotes

DRUG OR POISON	ANTIDOTES
Acetaminophen	*N*-acetylcysteine
Anticholinergics	Physostigmine
Anticholinesterases	Atropine
Benzodiazepines	Flumazenil
Black widow spider bite	Equine-derived antivenin
Carbon monoxide	Oxygen (100% or hyperbaric)
Coral snake bite	Equine-derived antivenin
Cyanide	Amyl nitrite, sodium nitrite, sodium thiosulfate, oxygen
Digoxin	Digoxin-specific Fab antibody fragment
Ethylene glycol	Fomepizole, ethyl alcohol
Isoniazid	Pyridoxine
Heavy metals (arsenic, copper, Dimercaprol [BAL], gold, lead, mercury)	EDTA, penicillamine
Hypoglycemic agents	Dextrose, glucagon, octreotide
Isoniazid	Pyridoxine
Methanol	Ethanol or fomepizole, folic acid
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphate	Atropine, pralidoxamine
Rattlesnake bite	Equine-derived antivenin

(Adapted from B. Mokhlesi, J.B. Leikin, P. Murray, T.C. Corbridge, Adult toxicology in critical care: Part I: general approach to the intoxicated patient, Chest 123 [3] [2003] 897–922.)

LABORATORY EVALUATION

A few measurements that are commonly done in the emergency room can give a hint about the nature and amount of the toxin ingested. Three simple calculations are most helpful in determining the type of ingestion: anion gap, osmolar gap, and oxygen saturation gap.[3] The anion gap and osmolar gap are most relevant to our discussion and will be discussed below. A review of the oxygen saturation gap can be found elsewhere.[3]

Anion Gap

The calculation of the difference between the measured cations and the measured anions can be used to estimate the difference between the *unmeasured* anions and the *unmeasured* cations.[31] The normal anion gap is 8 to 12 mEq/L, and a value above 12 mEq/L can signify an increase in unmeasured anions.[32] The most common intoxications to cause a high anion gap acidosis are ethylene glycol, methanol, and salicylates.[33] Also, an elevated anion gap from lactic acidosis can signify an intoxication with acetaminophen, carbon monoxide, metformin, cyanide, and nonsteroidal anti-inflammatory drugs (NSAIDs).[34] It is important to note that a normal anion gap does not rule out an intoxication, because many toxins do not cause a gap or there may be a coexisting condition that lowers the gap.[33] The most common condition to lower the gap is hypoalbuminemia: the anion gap falls 2.5 mEq/L for every 1 g/dl drop in serum albumin.[35] A few toxins such as methanol and ethylene glycol need to be metabolized before they create an anion gap acidosis. In these cases, intoxication may not be associated with an anion gap early on, especially when there is ethanol coingestion.[5]

Osmolar Gap

Ingestion of low molecular weight toxins will increase the difference between the measured and the calculated plasma osmolarity or osmolar gap. The calculated osmolarity

$$= 2 \times Na^{+} + \text{blood urea nitrogen}/2.8 + \text{glucose}/18 + \text{ethanol}/4.6$$

$$\text{Osmolar gap} = \text{measured Osm} - \text{calculated Osm}$$

An osmolar gap greater than 10 mOsm indicates the presence of osmotically active substances such as ethanol, methanol, isopropyl alcohol, and ethylene glycol.[36]

TABLE 51-3 Osmolar Contribution of Various Toxins and Drugs

AGENT	OSMOLAR GAP (mOsm/L)	SERUM CONCENTRATION (mg/dl)
Acetone	10	58
Ethanol	10	46
Ethylene glycol	10	62
Glycerol	10	92
Isopropanol	10	60
Mannitol	10	182
Methanol	10	32
Propylene glycol	10	76
Sorbitol	10	182

Serum concentration required to produce an osmolar gap of 10. See text for explanation.

Hospitalized patients may develop an osmolar gap from glycerol, intravenous (IV) immunoglobulin, propylene glycol, radiocontrast media, and sorbitol.[37] Propylene glycol is a common vehicle for intravenous medications and can cause an osmolar gap. Its metabolite, lactic acid, can contribute to a high anion gap acidosis.[38] Accumulation of propylene glycol in patients receiving high doses of IV medications such as diazepam, which have propylene glycol as their carrier, may lead to severe acidosis with hemodynamic instability.[39] Rarely this may require treatment with hemodialysis.[39] Table 51-3 lists the contribution to the osmolar gap of various drugs and toxins. The table displays the expected concentration of a substance in mg/dl that would cause an osmolar gap of 10 mOsm/L.

A number of toxins such as ethylene glycol and methanol will no longer produce an osmolar gap as they are metabolized, and in these cases, a normal gap does not exclude intoxication, only a late presentation.[5] Another factor that lowers the sensitivity of the osmolar gap is the considerable variation in the normal osmolar gap in the general population. Indeed, patients may have an increased gap that is still below 10 mOsm/kg.[40] Thus a high osmolar gap is supportive of intoxication, but a normal gap does not rule it out. On the other hand, the osmolar gap can also be falsely elevated. Patients who are critically ill may have an elevated gap because of the presence of endogenous substances such as amino acids.[41] Patients with hyperlipidemia or hyperproteinemia will have spurious hyponatremia leading to an elevated gap.[42] There is also an accumulation of osmotically active substances in chronic renal failure.[43] For all these reasons, the osmolar gap should be used with caution as additional evidence of an alcohol intoxication but should not be used as the primary determinant of intoxication or as a screening test.[44]

PHARMACOKINETICS OF TOXIN REMOVAL

To determine how well a specific extracorporeal technique will remove a specific drug or toxin, one should consider both dialysis-related factors and drug-related factors. The characteristics of a drug that determine whether it can be removed by a specific extracorporeal technique are molecular weight, protein binding, volume of distribution (V_d), lipid or water solubility, rate of equilibration with the vascular space, charge, and membrane binding.[45] The extracorporeal method (i.e., hemodialysis, peritoneal dialysis, or hemofiltration) also influences drug or toxin removal. Some of the important properties of the hemodialysis system that will be discussed are properties of the dialysis membrane, blood flow rate (Q_b), dialysate flow rate (Q_d), pH, and temperature.[46]

Drug-Related Factors

Molecular Weight

The molecular weight of a compound is the most reliable predictor of drug removal by a dialysis system. The molecular size, which comprises the molecular weight, shape, charge, and steric hindrance of a molecule, is also an important determinant of the molecule's ability to permeate a dialysis membrane pore.[47] Low-molecular-weight compounds or small molecules are those classified as being less than 500 Da. These molecules cross conventional low-flux (low porosity, low surface area) dialysis membranes readily, with the extent depending more on Q_b, Q_d, and effective membrane surface area. The clearance of these drugs is usually fairly close to the clearance of urea. For drugs that have low protein binding (to be discussed later), the clearance constant for these drugs can often be estimated as equal to the clearance constant of urea that is listed for the dialysis membrane being used.[48] High-molecular-weight compounds or *large solutes* are those greater than 5000 Da; they diffuse very slowly or not at all across membranes.[49] Middle-molecular-weight compounds are those between 500 and 5000 Da. Their removal is intermediate to the other two categories mentioned. Vancomycin, which has a molecular weight of 1500 Da, and vitamin B_{12}, with a molecular weight of 1355 Da, are good examples of a middle-molecular weight compounds.[50]

Drugs with molecular weights of more than 1000 Da depend more upon convection for dialytic clearance and are substantially removed only with high-flux dialysis, where there is a higher rate of water movement across the membranes.[51] Common features of high-flux dialysis membranes include high urea clearance constants at high blood flows, high ultrafiltration coefficients ($(K_{Uf}) > 15$ ml/mm Hg/hr), and higher vitamin B_{12} clearance. The vitamin B_{12} clearance for a dialysis membrane is often given as an estimate of its ability to clear middle-molecular weight compounds.[48] Removal of large solutes is enhanced by the use of a high flux filter with a porous membrane.[52] Over the past 5 years, there has been a trend toward the use of higher flux dialysis membranes.[53] Most membranes in use today have considerably higher ultrafiltration fractions, are more porous, and have higher clearance of vitamin B_{12} as compared to filters used 5 years ago, allowing for greater clearances of middle-molecular-weight compounds.[53] Evidence for this increase in middle-molecular weight clearances can be seen with the change in the dosing of vancomycin. It is now routine to need to dose vancomycin after each dialysis session when 5 to 10 years ago, it was dosed every 4 days or more for patients on dialysis.[54]

Protein Binding

The degree of protein binding of a drug or toxin will influence its clinical effect and its metabolism and excretion.[49] Protein binding renders the drug or compound pharmacologically inactive; only the unbound fraction of the drug can be readily metabolized and excreted by the liver or kidney or filtered by a dialysis membrane.[55] Only an unbound drug is pharmacologically active because only a free drug can cross the cell membrane and exert its pharmacological effect.[56] The protein-drug complex is too large to cross the dialysis membrane and is therefore poorly cleared by conventional dialysis.[47] Hemoperfusion and albumin-dialysis are more effective at removing drugs and toxins that are highly protein bound.[57]

Malnutrition and proteinuria lower serum protein levels and therefore lead to a higher fraction of free drug owing to a reduced number of protein binding sites. Also, AKI, chronic kidney disease (CKD), and critical illness can change the degree of protein binding.[58] The effect on protein binding by these clinical states depends on the illness and the drug in question. Medications that are acidic, such as penicillins, cephalosporins, phenytoin, furosemide, and salicylates, are most severely affected by the reduced protein binding in CKD.[59] Acidic drugs are bound to albumin, plasma concentrations of which are often decreased in uremic patients.[60] Conversely, alkaline drugs (e.g., propranolol, morphine, oxazepam, vancomycin) bind primarily to nonalbumin plasma proteins, such as α_1-acid glycoprotein (AAG). AAG is an acute-phase protein whose plasma concentrations are often elevated in renal dysfunction and acute illness.[61] Finally, as the dose of a drug increases, the level of protein binding may decrease, as in salicylate toxicity.[62]

In some cases, protein binding may change because of competition for binding sites by other drugs, metabolites, and accumulating endogenous substances. These other substances can displace medications from plasma protein binding sites.[59] One such example is CKD-induced accumulation of hippuric acid with a resultant inhibition of theophylline protein binding.[63] Another example is the increase in free fatty acids in critical illness or heparin use. Free fatty acids can compete with drugs such as tryptophan, sulfonamides, salicylates, furosemide, phenytoin, benzodiazepine, and valproic acid for protein binding sites.[64] Free fatty acid levels can change in a number of disease states such as critical illness, shock, and with the use of heparin during dialysis.[65] Heparin use during dialysis stimulates the activity of lipoprotein lipases, subsequently increasing free fatty acid levels by triglyceride breakdown. This increases the free fraction of the previously mentioned drugs during the time that heparin is in use.[66] Changes in protein binding of a drug can have a significant clinical effect in the setting of highly protein bound drugs with a narrow therapeutic index such as theophylline.[59] Table 51-4 displays the protein binding of the drugs and toxins discussed in this chapter.

Volume of Distribution

A drug or toxin's V_d is derived by dividing the total amount of drug in the body by its plasma concentration.[56] It should be noted that this ratio often does not refer to a specific anatomical compartment in the body, especially when it is large (i.e., > 1 L/kg).[56]

TABLE 51-4 Characteristics of Drugs and Toxins that are Amenable to Removal with Extracorporeal Therapy

AGENT	MOLECULAR WEIGHT (g/mol)	PROTEIN BINDING* (%)	VOLUME OF DISTRIBUTION L/kg
Methanol	32	<10	0.6
Ethylene glycol	62	<10	0.6
Isopropanol	60	<10	0.6
Salicylate	180	80	0.2†
Lithium	73	<10	0.8
Theophylline	180	60	0.3†
Phenytoin	252	90	0.5†
Carbamazepine	236	75	0.6†
Valproic acid	144	95	0.2†
Phenobarbital	232	50	0.9†

*Protein binding will decrease in toxic ingestion and other clinical states mentioned in text.
†These agents will have higher V_d with toxic ingestion.

$$V_d\ (L) = \text{dose}\ (mg)/Cp\ (mg/L)$$

V_d may be affected by a number of physiological determinants, including plasma protein and tissue binding, lipid partitioning, active transport systems, and overall body composition. A large V_d implies a high degree of tissue binding. Drugs and toxins that have high lipid solubility will have a high V_d as well. They are likely to be able to diffuse more rapidly into the brain and are usually cleared poorly by the kidney or hemodialysis.[47]

The drugs and toxins that have a V_d of less than 1 L/kg are usually water soluble and have low tissue binding and lipid solubility.[56] Drugs that meet these criteria include the alcohols (ethanol, ethylene glycol, methanol, and isopropyl alcohol), salicylates, lithium, theophylline, aminoglycosides, and most cephalosporins.[49] These drugs are more likely to be amenable to removal with extracorporeal techniques.[47] Table 51-4 displays the V_d of toxins and drugs discussed in this chapter.

Compounds with a high V_d with a high degree of tissue binding are not substantially removed by hemoperfusion or hemodialysis.[67] Some drugs and toxins that are known to cause severe toxic syndromes in overdose but are not well removed by extracorporeal therapy because of their high V_d include most antiarrhythmics (i.e., amiodarone, flecainide, and quinidine), most beta blockers, calcium channel blockers, chloroquine, colchicine, diazepam, digoxin, metformin, and tricyclic antidepressants.[68] In all of these cases, V_d is 2 L/kg or greater. Even in the case where the compound crosses the extracorporeal membrane easily and the plasma that passes the device is cleared of the toxin, only a small fraction of the total body burden is removed because it is bound to the tissues or lipids and is not accessible to the device.[69]

The V_d of a compound can change in a number of disease states and other circumstances. In cases such as AKI, CKD, and critical illness where the protein binding of the drug changes, drugs with a high degree of protein binding will have a change in their volume of distribution.[56] As the protein binding goes down, the volume of distribution will usually increase. Most water soluble agents will have a further increase in V_d in AKI as the total body water increases.[70]

The total drug taken and the chronicity of the ingestion can also influence the V_d in overdoses. For example, the V_d of salicylates increases in a toxic ingestion and with chronic ingestion. The former is due to a decrease in protein binding, and the latter is due to an increased tissue binding.[71] The fraction of unbound drug in the blood and tissue can influence the V_d.[55] In patients with impaired plasma protein binding, there is an increase in the apparent V_d of the drug. This is seen in patients with renal failure, owing to decreased albumin and impaired binding capacity of albumin. Renal failure decreases the V_d for digoxin but increases the V_d for phenytoin.[55]

Vascular Equilibration

Even for substances with a small V_d (i.e., $V_d = 0.6$ L/kg), most of the compound is outside the vascular space. The proportion of a compound that is extravascular increases with increasing V_d. After an ingestion, the substance's concentration in the vascular space will often decline following first order kinetics such that the proportion change in concentration over time remains the same.[56] This first order elimination suggests that the compound is in pseudoequilibrium between the movement into the vascular space and elimination out of the vascular space. This movement takes time, and with rapid removal of the drug from the vascular space, the pseudoequilibrium will be disturbed as the substance is removed from the vascular space faster than it can be replaced from extracellular and cellular stores (i.e., no longer following first order kinetics). With discontinuation of the extracorporeal elimination, there will be a rebound in the concentration as the movement into the vascular space catches up.[72] The degree of rebound increases with V_d, the degree of tissue binding, and inversely with the rate of clearance of the drug from the vascular space.[73] It is not a concern in continuous therapies.[74]

It is important to keep in mind the degree of rebound that is likely when reviewing literature on the effectiveness of an extracorporeal therapy to treat a drug intoxication. A report of a significant drop in concentration of a drug with therapy may just represent a disruption in the pseudoequilibrium between the intravascular space and the tissues. The important data is the fraction of the total drug burden removed and is best determined by measuring the drug in the effluent.[75] There are a number of reports of success with removing toxins with high V_d and slow tissue equilibration such as tricyclic antidepressants or metformin but in most cases, the authors report concentrations drawn after termination of the technique and not fraction of the drug removed.[76] Lithium has an intermediate V_d (0.8 L/kg) and slow equilibration into the vascular space. Although hemodialysis is effective at removing lithium in intoxication, the rebound can be significant following termination of the therapy and repeated treatments with hemodialysis or the use of a continuous therapy may be necessary.[77]

Device-Related Factors

In addition to drug or toxin characteristics, the effectiveness of the extracorporeal removal is also determined by the properties of the extracorporeal device. How effectively does the device remove the toxin from the plasma delivered to the device? The extraction ratio and the clearance rate are measures of the efficiency of the device.

Extraction Ratio and Clearance Rate

The extraction ratio (ER) is determined by measuring the concentration of the drug (plasma or blood levels) before it enters the hemoperfusion cartridge or hemodialyzer filter (A) and just after it exits (V). The ER can refer to the removal or the extraction of a drug from whole blood or plasma. It is calculated by the following formula:

$$ER = A - V/A$$

A value of 1 indicates that the drug was completely removed (extracted) in one pass through the extracorporeal system.[46] The clearance rate (Cl) is a measure of the rate at which blood or plasma is cleared of the substance by the device in a given time. The Cl can thus be calculated by knowing the flow rate (blood or plasma) through the system:

$$Cl = \text{flow rate} \times ER$$

It is important to differentiate between a high extraction ratio and effective total drug removal. A high clearance rate is necessary but not sufficient for effective removal of a drug. This will be discussed later.

Effective Extracorporeal Elimination

As stated earlier, efficient removal of a toxin from the plasma or blood is necessary to have effective elimination of the drug from the patient, but it is not sufficient.[75] The pharmacokinetics of digoxin will help illustrate this concept. The V_d of digoxin is approximately 10 L/kg.[78] If a 70 kg man ingests a toxic dose of one hundred 250 mcg tablets of digoxin, his plasma level would be approximately 36 mg/L after distribution to tissues.[56] Hemodialysis has a fairly high ER for digoxin, but even if we assume an ER of 1 with a plasma flow of 200 ml/min, the total removal of digoxin would be small after 4 hours.[79] In this case, the Cl = 200 ml/min or 48 L per 4 hour dialysis session. At most, this would remove 48 L × 36 mcg/L = 1.7 mg or 7% of the total dose. The actual removal of digoxin is even less because of the slow equilibration of digoxin from tissue stores.[78] In the case of digoxin, the ER is sufficiently high, but because of characteristics of the drug (i.e., high V_d and slow tissue equilibration), hemodialysis is not an effective therapy for digoxin toxicity, and the antidote digoxin immune Fab needs to be used to bind the drug.[80]

In summary: extracorporeal techniques are directed at the compound available in the plasma or blood. For the device to work effectively, the following conditions must be met:

1. There most be a high clearance rate of the compound from the blood.
2. A large proportion of the compound must be intravascular (i.e., small V_d).
3. The compound must equilibrate quickly from tissue stores to the vascular compartment.

As discussed earlier, the clearance rate is determined by a combination of drug and device characteristics. The drug characteristics include low protein binding and small size. As follows, we will discuss the device characteristics.

Hemodialyzer Properties

For hemodialysis, the factors that determine the clearance rate are membrane permeability, surface area of the membrane, Q_b, and Q_d.[45] Solute removal during hemodialysis is accomplished primarily by diffusion, with a smaller contribution coming from convection. Convection becomes a little more important with high flux dialysis membranes. To maximize clearance of a compound, one would pick a large permeable membrane with high Q_b and Q_d.[81] A high efficiency membrane is able to support higher blood and dialysis flows and achieves higher urea clearance. A high flux membrane is more permeable to middle molecules and allows for clearance of toxins with higher molecular weights. Most dialysis membranes in use today are high efficiency and high flux and therefore maximize the clearance rate of small and middle molecular weight compounds.[82] Clearances for small, unbound toxins can approach 300 cc/min with a high efficiency membrane given high Q_b and Q_d.[52]

Peritoneal Dialysis Properties

Clearance rates for peritoneal dialysis are significantly less than for hemodialysis and are rarely adequate to obtain significant toxin removal.[75] The factors in peritoneal dialysis that contribute to drug or toxin removal are as follows: 1) Transport characteristics of the peritoneal membrane; 2) composition of the dialysate solution; 3) frequency of exchanges; and 4) dwell times.[83]

Hemofiltration Properties

For hemofiltration, the solutes, drug, or toxin is removed primarily by convective mass transfer. As such, solutes dissolved in plasma water are removed in the filtrate. Most small molecules will cross the membrane close to their concentration in the serum. The sieving coefficient (S) is the ratio of the concentration in the ultrafiltrate to that in the serum.

$$S = C(f)/C(p)$$

Where C(f) is concentration in ultrafiltrate and C(p) is concentration in plasma. The sieving coefficient is usually close to 1 for small, non–protein-bound molecules. The Cl is proportional to the sieving coefficient and the ultrafiltration rate:

$$\text{Clearance rate} = \text{ultrafiltration rate} \times \text{sieving coefficient}$$

Thus toxin removal depends on high rates of ultrafiltration.[84]

Hemoperfusion Properties

Hemoperfusion allows for the removal of compounds by direct contact with a material that adsorbs the compound.[85] The material that acts as the sorbent is activated charcoal.[86] Unlike with hemodialysis, hemoperfusion is able to remove highly protein-bound and lipophilic compounds. The extraction ratio for most toxins approaches 1, and the Cl is therefore mostly determined by the Q_b.[87] To maintain this high ER, the activated charcoal cartridge needs to be changed after a few hours of therapy.[86] Clearance rates of over 200 cc/hr have been described for many toxins.[87] Because of superior blood flows with hemodialysis, however, compounds with good ER in hemodialysis will have better Cls for hemodialysis compared to hemoperfusion.[46]

INDICATIONS FOR EXTRACORPOREAL THERAPY

Indications for extracorporeal elimination of drugs or toxins depend most strongly on the clinical severity and potential complications of the poisoning. The following issues must be considered:

1. Characteristics of the individual patient: does the patient have impaired endogenous clearance of the toxin (e.g., older age, decreased renal function, congestive heart failure, liver failure), and is he or she more likely to have clinical toxic effects from the compound (e.g., older age, chronic ingestion, critically ill)?[3]
2. Characteristic of the compound: What are the toxic effects of the substance ingested, are there antidotes available, and are the adverse effects likely to be severe, permanent, or life-threatening?[46]
3. Characteristic of the ingestion: Was it a toxic dose, what is the plasma concentration, how is the level changing with time, and is it likely to go up over time or fail to fall?

Appropriate interpretation of the drug concentration must take into account hepatic or renal elimination, delayed GI absorption, active metabolites, altered distributional characteristics, and saturable elimination pathways. Extracorporeal elimination that increases the total body clearance by 30% or more is believed to be a worthwhile intervention in the proper clinical setting.[75]

Extracorporeal therapy may be considered when all of the following conditions are met:

1. The ingestion is likely to cause severe morbidity or mortality, and the removal of the drug from the serum will lessen this risk. In some intoxications the effect is too rapid and irreversible for extracorporeal removal to help (e.g., cyanide), or the removal from the serum does not remove it from the tissues where it has its toxic effect (e.g., paraquat).[88] Keep in mind the patient characteristics that may make the risk of severe toxic effects more likely such as older age or chronic ingestion in salicylate and theophylline ingestions.[89]
2. The extracorporeal therapy will add significantly to the total body elimination of the drug (>30%). In this case, the device must have a high Cl for the compound and the compound must be mostly in the vascular space (i.e., V_d = 0.6 L/kg) or equilibrate into the vascular space quickly. In some cases, this condition might be met partly because of a decreased endogenous clearance in the patient in question. A patient with lithium toxicity may be more likely to benefit from hemodialysis when there is impaired renal clearance because of heart failure or liver or kidney disease.[90]

There is some controversy about which poisons are likely to respond to extracorporeal therapy. Those for which there is some consensus regarding effectiveness of extracorporeal therapy are listed in Table 51-4 with their important characteristics.

SPECIFIC TOXINS

The rest of the chapter will focus on specific toxins and drugs that are frequent causes of intoxication and whose elimination is significantly enhanced with either hemodialysis or

TABLE 51-5 Exposures and Fatalities from Toxins that are Substantially Removed by Extracorporeal Techniques

TOXIN	EXPOSURES (% OF TOTAL)	FATALITIES (% OF TOTAL)	MORTALITY % OF EXPOSURES
Methanol	2086 (0.09)	8 (0.56)	0.38
Ethylene glycol	6135 (0.3)	34 (2.4)	0.55
Isopropyl alcohol	10,016 (0.4)	0 (0)	0
Salicylates	43,692 (1.82)	16 (1.13)	0.04
Lithium	5674 (0.24)	7 (0.49)	0.12
Theophylline	413 (0.02)	1 (0.07)	0.24
Phenytoin	3812 (0.16)	1 (0.07)	0.03
Carbamazepine	4357 (0.18)	2 (0.14)	0.05
Valproic acid	8627 (0.36)	1 (0.07)	0.01
Phenobarbital	2368 (0.1)	2 (0.14)	0.08

(Data from A.C. Bronstein, D.A. Spyker, L.R. Cantilena Jr., et al., 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System [NPDS], Clin. Toxicol. [Phila] 45 [8] [2007] 815–917.)

hemoperfusion. Toxins in which hemodialysis is likely more effective include ethanol, methanol, ethylene glycol, isopropyl alcohol, salicylates, and lithium. Other drugs such as theophylline, phenytoin, carbamazepine, valproic acid, and phenobarbital have a higher degree of protein binding and may benefit from hemoperfusion compared with hemodialysis. Table 51-5 shows the number of reported exposures and the mortality rates for these toxins as reported to TESS in 2006.

OVERVIEW OF ALCOHOLS

The alcohols (i.e., ethyl alcohol, methanol, ethylene glycol, and isopropyl alcohol) all have drug characteristics that allow for rapid removal with hemodialysis. They all have low molecular weights, are hydrophilic, have small V_d, and rapidly equilibrate with the intravascular space.[5] The drug characteristics of these compounds are listed in Table 51-4. Ethanol toxicity usually does not require hemodialysis because most patients will recover with supportive measures alone.[91]

Estimating Serum Levels in Alcohol Intoxication

As discussed earlier, the alcohols will produce an osmolar gap when they are present in the serum in significant amounts.[92] Although there are some cautions to be noted with its use, the osmolar gap can be used to estimate the serum concentration of the alcohols.[36] If one keeps in mind that the osmolar gap may have fairly low specificity and sensitivity for the detection of alcohol intoxication because of variations in the normal gap in the general population, it can be helpful as a rapid way to estimate serum levels of the intoxicant.[93] It should not be used as the sole criteria for deciding a treatment strategy in the case of a possible intoxication with one of the alcohols, but it can be useful when other clinical data support the diagnosis.[5]

Table 51-3 describes the use of the osmolar gap to estimate the serum level of the alcohol intoxicant. An increase in the osmolar gap of 10 mOsm/L would be expected to be caused by a concentration of the drug listed in the table. For example, if methanol were to cause an increase in the osmolar gap of 10 mOsm/L, then the expected concentration of methanol would be 32 mg/dl. To estimate the concentration of the agent listed, the osmolar gap divided by 10 is multiplied by the factor listed in the table for the specific alcohol. It is important to remember that a low gap does not always imply a low risk of intoxication. First, the gap will underestimate serum levels in some people who start out with a low serum osmolarity.[93] Second, the gap will fall as the alcohol is metabolized, and in the case of ethylene glycol and methanol, the metabolites are toxic, and therefore a patient with a low gap may still have an indication for aggressive therapy including dialysis.[94]

Estimating Dialysis Time for Alcohol Intoxications

Since the alcohols all have small V_d and rapid equilibration with the vascular space, their elimination closely follows first order kinetics during dialysis.[5] The elimination of all the alcohols will follow the formula for first order kinetics:

$$C_1/C_0 = e^{-kt/V}$$

Where C_1 is the concentration at the end of dialysis, C_0 is the concentration at the start of treatment, k is the clearance constant for the dialysis session, t is the time in minutes, and V is the V_d of the alcohol.[95] The clearance constant for dialysis of the alcohols (k) can be estimated as fairly close to the urea clearance constant for the dialyzer and will be found in the literature sent with the dialyzer. It is recommended that k is estimated at 80% of the manufacturer defined urea clearance rate to avoid overstating achievable clearances.[95] With a high-efficiency membrane, high Q_b, and Q_d, the clearance constant can approach 0.3 L/min.[5]

If we determine a final concentration C_1 that we want to achieve, we can solve for the time required for dialysis to achieve this final concentration:

$$t\ (\text{min}) = -\ln (C_1/C_0) \times V_d\ (\text{L})/k\ (\text{L/min})$$

As an example, if a 100 kg man has an ethylene glycol ingestion with a level of 80 mg/dl and we want to perform dialysis with a membrane that can deliver a k = 0.3 L/min until his level is less than 20 mg/dl then:

$$t = -\ln (20/80) \times 60\ \text{L}/0.3\ \text{L/min} = 277\ \text{min} = 4\ \text{hrs}\ 37\ \text{min}$$

It is important to note that this estimation does not take into account endogenous clearance of the alcohol and therefore will overestimate the time needed if the patient has significant renal clearance.[95]

Ethanol

Ethanol is rapidly metabolized without toxic metabolites. Alcohol dehydrogenase metabolizes ethanol to acetaldehyde primarily in the liver.[96] The enzyme is saturable, and therefore the metabolism does not follow first order kinetics, and it is meaningless to speak of a half-life. The metabolism in most patients is 15 to 25 mg/dl/hr.[97] Most patients will display toxic symptoms with levels are greater than 150 mg/dl, and most lethal ingestions are with levels of greater than 400 mg/dl.[98] When ethanol is coingested with another alcohol, the ethanol level must be included in the calculation of the osmolar gap.[5]

The clearance of ethanol with dialysis is excellent and will increase total removal of ethanol by 4 to 5 times.[99] The higher the ethanol level, the greater the advantage of hemodialysis over endogenous clearance. However, hemodialysis is rarely required in ethanol intoxication, and most patients respond to supportive measures.[98] The removal of ethanol with hemodialysis must be accounted for when ethanol is used as an antidote in ethylene glycol and methanol intoxication, and in those cases, the dose must be increased during dialysis.[100]

Methanol

Methanol is a highly toxic alcohol that is found in a variety of commercial products, including antifreeze, windshield wiper fluid, some racing car fuels, paint thinner, and canned solid fuel for keeping food warm.[101] There were eight reported deaths from 2086 exposures to methanol in 2006.[1] The estimated minimum lethal dose for adults is approximately 15-30 ml.[102] There are also reports of patients surviving ingestions greater than 400 ml without sequelae.[103]

Pharmacokinetics of Methanol

Methanol is rapidly absorbed after ingestion. As listed in Table 51-4, it has a V_d of 0.6 L/kg and a molecular weight of 32 g/mole.[38] The metabolism of methanol to its products is displayed in Figure 51-1. Methanol is oxidized by alcohol dehydrogenase in the presence of nicotinamide adenine dinucleotide (NAD) to formaldehyde. Formaldehyde is then quickly oxidized to formate.[104] The metabolism of formate is slow, and therefore formate will accumulate with even a small dose of methanol.[105] Formate produces much of the toxic effect and the high anion gap acidosis. The formation of lactate also contributes to the anion gap acidosis. Pyruvate is metabolized to lactate because of the reduction of NAD to NADH during the oxidation of methanol.[5] Ethanol and fomepizole will slow the oxygenation of methanol by inhibiting alcohol dehydrogenase.[106]

Clinical and Laboratory Findings in Methanol Intoxication

Table 51-6 lists the important findings in methanol intoxication. Most of the clinical effects of methanol intoxication are due to the accumulation of formate.[102] Before it is metabolized, methanol's major effect is to cause central nervous system (CNS) depression.[107] This is of short duration and is followed by a latent period. The latent period, which lasts 14 to 18 hours, is due to the time it takes for alcohol dehydrogenase to metabolize methanol to formate and for formate to accumulate.[105] The latent period will be prolonged with ethanol coingestion or with fomepizole treatment.[106]

The latent period is followed by a number of systemic findings as formate accumulates. The prognosis in methanol intoxication depends on the existence of the effects of the formate accumulation and patients who present with severe acidosis, seizure, or coma due to the formate have an increased mortality compared to patients without these signs on presentation.[5] Metabolic acidosis can be severe, and a pH of less than 7 has been found to be the strongest predictor of mortality. Patients with a pH of less than 7 have 20 times the mortality compared to patients with pH of greater than 7.[107] CNS effects in this stage can include headache, lethargy, convulsions, delirium, and coma.[108] Patients who present with seizure or coma have more than 10 times the mortality of patients without these symptoms.[109] Serum methanol levels have very little prognostic value for either permanent visual changes or death.[109]

Most of the long-term morbidity due to methanol intoxication is related to the toxic effect on the retina and CNS.[110] Ocular findings can be prominent and may include photophobia, central scotoma, visual field defects, fixed pupils, and difficulty with light adaptation.[111] Pupillary dysfunction has also been shown to be a strong predictor of mortality.[109]

TABLE 51-6 Clinical Effects of Methanol Intoxication

TIME PERIOD		CLINICAL	LABORATORY
Early	CNS	Mild CNS Depression	Osmolar gap High methanol level
Latent period (12-24 hrs)			
Late	CNS	Vertigo, lethargy, coma, seizures, Parkinson like syndrome, putamen necrosis and hemorrhage	Anion gap metabolic acidosis due to formate and lactate Falling osmolar gap Falling methanol level
	Vision	Decreased acuity, photophobia, pupillary defect, hyperemia of optic disc, retinal edema, central scotoma, blindness	
	GI	Abdominal pain, pancreatitis, transaminitis.	
	Kidney	AKI (rare), myoglobinuria (rare)	

(Data from D.G. Barceloux, G.R. Bond, E.P. Krenzelok, et al., The American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning, American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J. Toxicol. Clin. Toxicol. 40 [4] [2002] 415–446.)

AKI, acute kidney injury; *CNS*, central nervous system; *GI*, gastrointestinal.

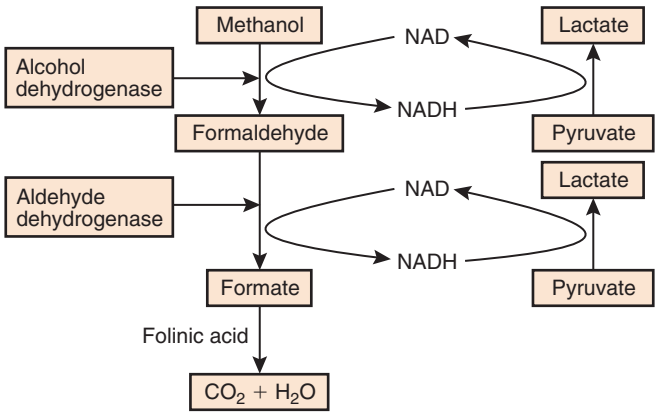


FIGURE 51-1 Metabolism of methanol to its toxic intermediates. See text for explanation.

Funduscopic signs can include hyperemia, disk edema, and optic atrophy.[112] The ocular findings are due to the direct cytotoxic effect of formate on the retina.[113]

The CNS effects can include bilateral hemorrhagic necrosis of the putamen with blindness, coma, or death.[114] Sudden death has occurred due to cerebral edema following hemorrhage, and a number of authors have proposed that heparin used in dialysis may increase this risk.[115] Patients who survive may develop a Parkinsonian like syndrome or a polyneuropathy as a late sequelae of the intoxication.[116] Other systemic findings can include nausea, vomiting, diaphoresis, and abdominal pain. The abdominal pain may be due to pancreatitis.[117]

The most prominent laboratory abnormality in methanol intoxication is an anion gap acidosis.[104] The acidosis is due to the accumulation of formate from the metabolism of methanol and an increase in the production of lactate.[118] As stated earlier, a severe acidosis (i.e., pH < 7) suggests a late presentation of a potentially lethal ingestion and is the strongest predictor of mortality.[104] A patient who presents early after an ingestion or later after an coingestion with ethanol may have little or no acidosis, making the diagnosis of methanol intoxication much more difficult.[119] These same patients receive the most benefit from alcohol dehydrogenase inhibition since the ingested methanol still needs to be metabolized to formate to have its toxic effect.[106] These patients tend to have a much better prognosis.[109]

Methanol also produces an osmolar gap. A serum level of 32 mg/dl increases the measured serum osmolarity by 10 mOsm/kg, and the serum methanol level can be estimated by multiplying the osmolar gap by 3.2 (see Table 51-3).[120] A high serum methanol level should therefore cause a gap between the calculated serum osmolarity and the measured osmolarity by freezing point depression. However, patients with methanol intoxication may have a normal gap (<10 mOsm/kg) if they present late after ingestion and the methanol has been converted to formate.[119] Formate does not contribute to the serum osmolarity because it is balanced by sodium, which is included in the calculated osmolarity. For this reason, the osmolarity gap should be used to help support the diagnosis of methanol intoxication, but it is not sensitive enough to rule out intoxication, when there is no gap.[36]

Supportive Therapy for Methanol Intoxication

Supportive treatment for methanol intoxication includes airway protection, circulatory support, correction of metabolic abnormalities, and control of seizures.[6] Bicarbonate is indicated for patients with a pH of less than 7.3.[121] The use of folate has not been rigorously studied in humans but has been shown to increase the metabolism of formate to carbon dioxide and water in animals.[122] It can be given as a 50 mg intravenous dose every 4 hours for 5 doses then once a day.[121] Symptomatic patients should be given one dose of 1 mg/kg of folinic acid intravenously.[123]

Bicarbonate based intravenous fluids should be given to all patients with acidosis due to methanol intoxication unless there is a contraindication to the volume. The use of bicarbonate based fluids may help patients in two ways. Often patients will present with some degree of volume depletion, and volume replacement will help maintain kidney function and allow for renal clearance of methanol and formate.[5] Bicarbonate is also indicated for patients with pH of less than 7.3 to help correct the acidosis.[121] The correction of the acidosis will decrease the ratio of formic acid to formate.[124] Formic acid likely has the greater toxic effect on mitochondrial cytochrome oxidase than formate. Therefore, in acidosis the increased ratio of formic acid to folate contributes to the drop in serum pH by promoting lactate production.[124] Compared to formate, formic acid also has a greater toxic effect on CNS and ocular tissue due to its ability to cross the cell membrane. A few studies have seen a correlation between improvement in ocular and CNS toxicity and correction of the acidosis in methanol intoxication.[125]

Inhibition of Alcohol Dehydrogenase: Ethanol and Fomepizole

The main objective of treatment of methanol intoxication is to limit the accumulation of formate. This is achieved by inhibiting alcohol dehydrogenase with either ethanol or fomepizole. Both have been shown to slow the metabolism of methanol to formate.[106] One of these two antidotes should be used as soon as possible to prevent the production of formate. Indications for the use of either ethanol or fomepizole include a serum level of greater than 20 mg/dl, a high osmolar gap after ingestion of methanol, or a high index of suspicion for methanol intoxication in a critically ill patient (Table 51-7).[121]

Ethanol has been used as an inhibitor of alcohol dehydrogenase in ethylene glycol intoxication for 50 years but has not been approved by the U.S. Food and Drug Administration (FDA).[126] The standard loading dose of ethanol is 0.6 g/kg followed by a constant infusion to keep the blood ethanol level between 100 and 200 mg/dl.125 The average maintenance dose of ethanol is 100 mg/kg/hr but is significantly higher for alcoholics and must also be increased while the patient is on dialysis.[127] Blood ethanol levels should be checked every 1 to 2 hours until a steady state has been reached and then every 3 to 4 hours (Table 51-8).[121] The potential adverse effects of ethanol include CNS depression, hypoglycemia, respiratory depression, and aspiration.[128]

Fomepizole should be given at a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 48 hours. After 48 hours, the dose should be increased to 15 mg/kg every 12 hours.[129] Fomepizole should be continued until the

TABLE 51-7 Indications for Fomepizole or Ethanol therapy in Methanol or Ethylene Glycol Intoxication

1. Serum level of ethylene glycol or methanol > 20 mg/dl
OR
2. History of ingestion of ethylene glycol or methanol and osmolar gap > 10 mOsm/L
OR
3. Strong suspicion of ingestion of ethylene glycol or methanol and at least 2 of the following:
a. Arterial pH < 7.3
b. Serum bicarbonate < 20 mEq/L
c. Osmolar gap > 10 mOsm/L
d. Calcium oxalate crystals in urine (in ethylene glycol ingestion)

(Adapted from D.G. Barceloux, E.P. Krenzelok, K. Olson, W. Watson, American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning, Ad Hoc Committee, J. Toxicol. Clin. Toxicol. 37 [5] [1999] 537–560.)

TABLE 51-8 Ethanol Dosing in Methanol and Ethylene Glycol Intoxications

Loading dose	600-700 mg/kg
Maintenance dose	66 mg/kg/hr continuous (nondrinker)
	154 mg/kg/hr (chronic drinkers)
Dose during HD	169 mg/kg/hr
	257 mg/kg/hr (chronic drinkers during HD)
Check ethanol levels every 1-2 hours until stable then every 3-4 hours	
Keep serum concentration between 100-150 mg/dl	
Continue until methanol or ethylene glycol level < 20 mg/dl HD, hemodialysis	

(Data from D.G. Barceloux, G.R. Bond, E.P. Krenzelok, et al., The American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning, American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J. Toxicol. Clin. Toxicol. 40 [4] [2002] 415–446.)

TABLE 51-9 Fomepizole Dosing in Methanol and Ethylene Glycol Intoxications

Loading dose	15 mg/kg
Maintenance dose	10 mg/kg every 12 hours for 48 hours
After 48 hrs	15 mg/kg every 12 hours
During hemodialysis	Increase frequency to every 4 hours
Continue until methanol or ethylene glycol < 20 mg/dl	

(Data from J. Brent, K. McMartin, S. Phillips, et al; Methylpyrazole for Toxic Alcohols Study Group, Fomepizole for the treatment of methanol poisoning, N. Engl. J. Med. 344 [6] [2001] 424–429.)

serum methanol level is less than 20 mg/dl and the patient is asymptomatic with a normal serum pH.[121] Fomepizole is removed with dialysis and therefore needs to be dosed every 4 hours during dialysis (Table 51-9).[130]

The dose of both inhibitors of alcohol dehydrogenase have to be increased during dialysis.[129] Fomepizole may be the preferred antidote in methanol intoxication because levels do not need to be followed, it has fewer side effects, does not cause further sedation and it has a much simpler dosing scheme both with and without concurrent dialysis.[131] Finally, because of the low side effect profile, some patients treated with fomepizole may not need observation in an intensive care unit (ICU) if they are otherwise stable without significant acidosis.[132] Other studies have found an increase in cost with the use of fomepizole and recommend the use of ethanol when feasible.[133] With either antidote, the treatment should be continued until the methanol level is undetectable or both symptoms and acidosis resolve and the level is less than 20 mg/dl.[121]

Hemodialysis for Methanol Intoxication

Hemodialysis is the extracorporeal therapy of choice in the treatment of methanol intoxication. It will remove both methanol and formic acid efficiently and will help correct the acidosis.[105] It should be considered in any patient with severe acidosis or other refractory metabolic disturbance, high formate levels, seizures, visual changes, funduscopic abnormalities, or mental status changes (Table 51-10).[121] The traditional indication for dialysis was a methanol level of greater than 50 mg/dl.[104] However, with the availability

TABLE 51-10 Indications for Dialysis in Patients with Methanol Intoxication

1. Metabolic acidosis with pH < 7.25-7.3
2. Vision or funduscopic abnormalities
3. Deteriorating vital signs, seizures, or mental status despite supportive care
4. Acute kidney injury
5. Refractory electrolyte imbalance
6. *Methanol level > 50 mg/dl* (No longer considered an indication in certain patients—see text)

(Data from D.G. Barceloux, G.R. Bond, E.P. Krenzelok, et al., The American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning, American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J. Toxicol. Clin. Toxicol. 40 [4] [2002] 415–446.)

of fomepizole, a less toxic antidote compared to ethanol, and since the serum methanol level has not been linked to permanent visual changes or death, some authors have argued that a high methanol level alone is no longer an indication for dialysis if no other indication for dialysis is present.[134] Withholding dialysis in patients with a high methanol level should only be considered if all of the following conditions are met:

1. The patient is receiving fomepizole.
2. The patient is clinically stable, awake, and alert.
3. The patient has normal kidney function.
4. The serum bicarbonate and anion gap are normal.
5. There is no evidence of end organ damage such as visual or funduscopic changes.[121]

Patients with a high methanol level that are not treated with dialysis should be watched closely for the development of acidosis or vision changes that would indicate the need for urgent dialysis.[121]

Clearance constants with high efficiency membranes have been as high as 250 ml/min for both formate and methanol.[135] The dose of both ethanol and fomepizole need to be increased during hemodialysis.[129] Hemodialysis can hinder the maintenance of adequate ethanol levels, and a number of authors have described the use of ethanol-enriched dialysate solutions.[136] Hemodialysis should be continued until the serum methanol level is undetectable or the patient has a normal serum pH and a level of less than 20 mg/dl.[121] If a rapid method for determining the methanol level is not available, the osmolar gap can be used as a surrogate level, and in that case, dialysis should be performed until the gap drops to normal.[137] In cases of very high methanol levels, treated with high-efficiency dialysis, there may be a small rebound (<20 mg/dl).[138] For this reason, the alcohol dehydrogenase inhibitor should be continued for a few hours after the termination of dialysis and the methanol level should be rechecked.[121] See estimating dialysis time for alcohol intoxication addressed earlier for an example of how to approximate the necessary dialysis time.

There are a couple of important possible complications of hemodialysis in methanol intoxication. The most drastic complication is brain hemorrhage.[115] This risk may due to the combination of the bilateral cerebral ischemia of the basal ganglia that can arise from formate toxicity and the use of heparin during dialysis.[139] It is not clear whether avoidance of heparin during dialysis would decrease the risk

of brain hemorrhage, but caution is warranted in the use of heparin in methanol intoxication.[115] Hypophosphatemia is a fairly common complication of prolonged hemodialysis for methanol intoxication. Phosphate can be given peripherally or a phosphate enriched dialysate may be used.[136] As stated earlier, hemodialysis can lead to inadequate alcohol dehydrogenase inhibitor levels if the dose of the antidote is not increased during therapy.[129]

Ethylene Glycol

Ethylene glycol is a sweet-tasting substance that is a common constituent of antifreeze and deicing solutions. It can also be found in hydraulic brake fluid, many solvents, and as an agent in chemical synthesis.[140] Because of its sweet taste and its ability to intoxicate, it is sometimes used as a substitute for ethanol.[141] Intoxication can also follow an accidental ingestion in children or as a suicide attempt. It accounts for approximately 0.3% of all exposures and 2.5% of all deaths due to poisonings.[1] In 2005, there were 6135 exposures to ethylene glycol and 34 deaths reported to TESS (see Table 51-5).[1] This is a mortality rate of 0.6%. The estimated minimum lethal dose for adults is approximately 100 ml.[140] A number of patients have survived ingestions of more than 2000 ml.[142] In a case report by Johnson and coworkers, one patient who underwent rapid treatment with ethanol infusion and hemodialysis in the emergency room survived an ingestion of 3000 ml without long-term sequelae. The ethylene glycol level was found to be 1889 mg/dl.[143]

Pharmacokinetics of Ethylene Glycol

Ethylene glycol reaches a peak serum level 2 to 4 hours after ingestion. It is water soluble and has a V_d that is equal to total body water (0.6 L/kg). It has a molecular weight of 62 g/mole.[144] Figure 51-2 displays the metabolism of ethylene glycol to its products. Ethylene glycol is oxidized by alcohol dehydrogenase in the presence of NAD to glycoaldehyde, which is then rapidly oxidized to glycolate.[5] Ethanol and fomepizole slow the metabolism of ethylene glycol by inhibiting the enzyme alcohol dehydrogenase.[145] Glycolate is the toxic metabolite and produces the high anion gap acidosis.[146] Glycolate may be metabolized to oxalate, α-hydroxy-β-ketoadipate, and glycine.[147] Oxalate causes some of the end organ damage as a direct toxin and through calcium oxalate deposition.[148] Some part of the acidosis stems from the production of lactate and is due to the reduction of NAD to NADH, which drives the conversion of pyruvate to lactate (see Figure 51-2).[149] Without treatment, the elimination half-life of ethylene glycol is 3 to 8 hours.[148] Ethanol and fomepizole will prolong the half-life five fold to 15 to 40 hours.[145]

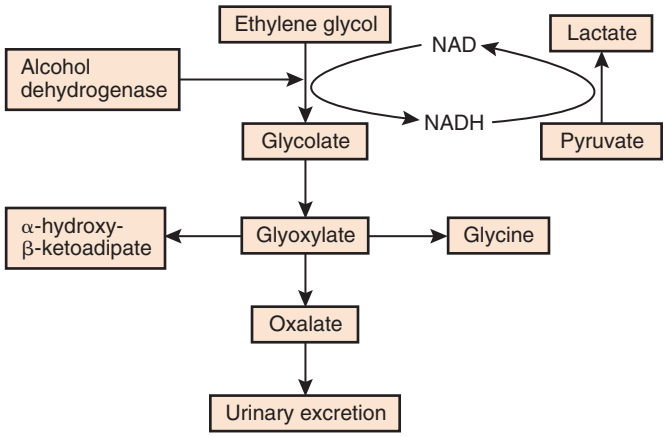


FIGURE 51-2 Metabolism of ethylene glycol. See text for explanation.

Clinical and Laboratory Findings in Ethylene Glycol Intoxication

The clinical course of ethylene glycol intoxication can be divided into three stages (Table 51-11).[150] The first stage occurs less than an hour after ingestion and is characterized by mental status depression similar to alcohol intoxication. In severe intoxication, coma, seizures, and respiratory depression can complicate this stage.[150] This stage lasts about 12 hours as the ethylene glycol is oxidized to glycoaldehyde and glycolate.[151] In the second stage, glycolate has a toxic effect on the cardiopulmonary system.[152] In severe intoxications, patients can develop acidosis, heart failure, pulmonary edema, or acute respiratory distress syndrome (ARDS).[153] The timing of this stage depends on the metabolism of the ethylene glycol to glycolate and usually starts about 12 hours after ingestion but will be delayed by alcohol coingestion.[154]

TABLE 51-11 Clinical Effects of Ethylene Glycol Intoxication

STAGE		CLINICAL	LABORATORY
1 (0.5-12 hrs)	CNS	Inebriation and euphoria	Osmolar gap High ethylene glycol level
2 (12-24 hrs)	CV	Tachycardia, hypertension, CHF, multiorgan failure	Anion gap metabolic acidosis due to glycolate and lactate Falling osmolar gap Falling ethylene glycol level
	Pulmonary	Hypoxia, ARDS	
3 (24-72 hrs)	CNS	Cranial neuropathy, seizures, hypotonia, coma	Hypocalcemia, leukocytosis, elevated creatine kinase.
	Kidney	Oliguria, AKI, flank pain, calcium oxalate crystalluria	
	GI	Hepatitis, ischemic bowel	
	Muscle	Myalgia	

(Data from D.G. Barceloux, E.P. Krenzelok, K. Olson, W. Watson, American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning, Ad Hoc Committee, J. Toxicol. Clin. Toxicol. 37 [5] [1999] 537–560.)
AKI, acute kidney injury; *ARDS,* acute respiratory distress syndrome; *CNS,* central nervous system; *CV,* cardiovascular; *GI,* gastrointestinal.

Review of data from TESS suggests that most deaths occur during this stage.[155]

The final stage occurs 24 to 72 hours after ingestion and is characterized by flank pain, acute tubular necrosis, hypocalcemia, and renal failure.[156] During this stage, the production of oxalate leads to calcium oxalate precipitation in the kidney and other tissues and hypocalcemia.[157] The renal toxicity is probably due to a combination of hydronephrosis from calcium oxalate crystals and a direct toxic effect from the metabolites of ethylene glycol.[158] Most renal damage is reversible, and renal recovery, which may take a few months, is the norm even after anuria.[158] The toxicity to other tissues due to calcium oxalate deposition include persistent cognitive and motor deficits, cranial neuropathy, polyradiculoneuropathy, ischemic bowel, hepatitis, and cardiac ischemia.[156]

There is very little correlation between serum ethylene glycol levels and clinical outcome.[147] Indeed, patients may have a very high mortality if they present after their serum levels have begun to decrease and the ethylene glycol has been converted to its toxic metabolites.[125] There is better correlation between the arterial pH, serum bicarbonate or glycolate level and the clinical outcome.[159] A number of studies of patients treated with fomepizole have shown that those who present without acidosis or a high glycolate level will do well.[147]

Ethylene glycol intoxication is characterized by a high anion gap acidosis, osmolar gap, and hypocalcemia.[153] The anion gap acidosis is due to both the production of glycolate and lactate. Lactate is formed because of the reduction of NAD to NADH during the oxidation of ethylene glycol to glycolate.[5] A patient may have no acidosis soon after ingestion before the ethylene glycol has been converted to glycolate. The acidosis will worsen as the ethylene glycol is metabolized.[150] Ethylene glycol will also form an osmolar gap because it is osmotically active and has a relatively small molecular weight. In ethylene glycol intoxication, the serum level of the toxin can be estimated by multiplying the osmolar gap by 6.2 (see Table 51-3).[160] An osmolar gap lacks the sensitivity and specificity to be an ideal screening test for intoxication.[93] Glycolate does not contribute to the osmolar gap so that as the ethylene glycol is metabolized to glycolate, the osmolar gap will in fact fall.[161] Therefore, patients who present late after an ingestion may have a normal osmolar gap.[162]

The urine may contain two forms of calcium oxalate crystals in ethylene glycol intoxication (Figure 51-3). The dumbbell-shaped monohydrate forms are more common, but the octahedral-shaped dihydrate form is more specific for ethylene glycol intoxication.[163] Individuals who ingest a large amount of vitamin C or urate-containing foods may have monohydrate calcium oxalate crystals in their urine. The dihydrate form requires higher oxalate concentrations for its formation and therefore is more indicative of intoxication with ethylene glycol.[125] If the ethylene glycol ingestion is in the form of antifreeze, the urine will often fluoresce under ultraviolet light because of the addition of fluorescein to most antifreeze preparations.[164]

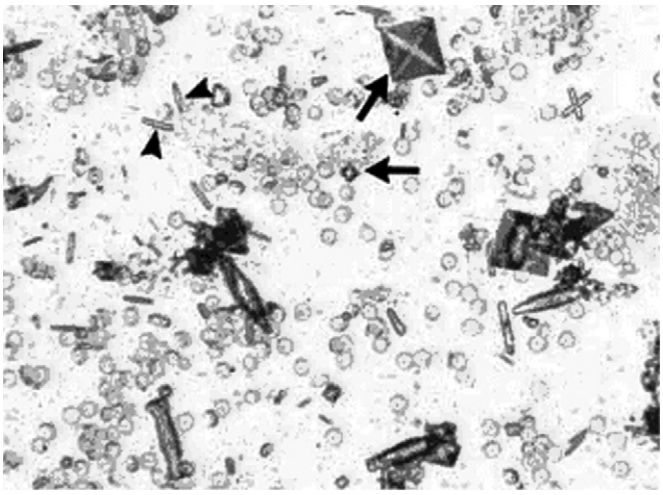


FIGURE 51-3 Urine from a patient after ethylene glycol ingestion. Shown are both types of calcium oxalate crystals. The *arrows* point toward the envelope-shaped dihydrate calcium oxalate crystal. The *arrowheads* point toward the needle-shaped monohydrate calcium oxalate crystals. (Used with permission from J.K. Takayesu, H. Bazari, M. Linshaw, Case records of the Massachusetts General Hospital. Case 7-2006. A 47-year-old man with altered mental status and acute renal failure, N. Engl. J. Med. 354 [10] [2006] 1065–1072.)

Supportive Therapy for Ethylene Glycol Intoxication

Supportive treatment includes airway protection, circulatory support, correction of metabolic abnormalities, and control of seizures.[6] Bicarbonate is indicated for patients with pH of less than 7.3.[147] Asymptomatic hypocalcemia is generally not treated because of the risk of increasing the formation of calcium oxalate crystals.[147] Seizures may be due to hypocalcemia but should be treated first with standard anticonvulsants.[165] There is no role for activated charcoal, cathartics, or gastric lavage in ethylene glycol intoxication.[147] Alcoholics and patients likely to be malnourished should be given thiamine and pyridoxine.[147] The addition of thiamine, 100 mg intramuscularly (IM) or IV, and pyridoxine, 50 mg IV every 6 hours, will shunt the metabolism of ethylene glycol to less toxic metabolites.[5] Thiamine promotes the metabolism of glyoxylate from glycolic acid to a nontoxic metabolite, α-hydroxy-β-ketoadipate, and pyridoxine promotes the metabolism of glyoxylate to glycine.[166]

Inhibition of Alcohol Dehydrogenase: Ethanols and Fomepizole

As with methanol intoxication, fomepizole and ethanol will slow the metabolism of ethylene glycol to its more toxic metabolites.[159] The indications for the use of one of the antidotes have been outline by the AACT. These indications include a plasma ethylene glycol concentration of greater than 20 mg/dl, a recent ingestion of ethylene glycol, and an osmolar gap greater than 10 mOsm/kg or a high clinical suspicion and two of the following: pH of less than 7.3, serum bicarbonate of less than 20 mEq/L, osmolar gap of greater than 10 mOsm/kg, or urinary oxalate crystals (see Table 51-7).[147] The dosing schedule of each antidote is the same as that for methanol intoxication and is listed in Tables 51-8 and 51-9.[106]

As with methanol intoxication, fomepizole may be the preferred antidote in ethylene glycol poisoning because of its ease of administration and because it does not cause CNS depression or hypoglycemia.[159] Some patients treated with fomepizole may not need observation in an ICU or hemodialysis if they have no acidosis and are otherwise

clinically stable.[167] Fomepizole is removed with dialysis and therefore needs to be dosed every 4 hours during dialysis.[159]

Hemodialysis for Ethylene Glycol Intoxication

Hemodialysis is very effective at clearing ethylene glycol and its metabolites. The clearance rate of ethylene glycol ranges between 200 and 250 ml/min depending on the filter Q_b.[145] Glycolate, which is the major toxic metabolite, has a half-life of up to 18 hours without hemodialysis, but the half-life is reduced by a factor of 6 with hemodialysis.[146] Patients with acidosis may therefore still benefit from hemodialysis, even in the face of a low serum ethylene glycol level, if they have an anion gap acidosis suggesting high glycolate levels.[125]

The indications for hemodialysis include those patients who have or are likely to develop the major sequelae of ethylene glycol ingestion. These include patients with metabolic acidosis (pH < 7.3) or deteriorating clinical status with respiratory failure or hypotension. Patients with acute renal failure and a metabolic derangement that is unresponsive to standard therapy should be considered for hemodialysis as well (Table 51-12).[147] In the past, an ethylene glycol level of 50 mg/dl was considered an indication for hemodialysis.[140] Recent experience suggests that patients with normal renal function and no acidosis may be treated with fomepizole without hemodialysis, even in the setting of an ethylene glycol level of greater than 50 mg/dl.[38] Withholding dialysis in patients with a high ethylene glycol level should only be considered if all of the following conditions are met:

1. The patient is receiving fomepizole.
2. The patient is clinically stable, awake and alert.
3. The patient has normal kidney function.
4. The serum bicarbonate and anion gap are normal.
5. There is no evidence of end organ damage such as neuropathy, ischemic bowel, or cardiac dysfunction.[38]

These patients would require close monitoring for the development of renal insufficiency or acidosis.[147]

Both fomepizole and ethanol are cleared during dialysis.[100] The addition of ethanol to the dialysate has been shown to maintain blood ethanol levels during dialysis.[136] The use of fomepizole during hemodialysis is more straightforward and only requires an increase in the frequency of the doses to every 4 hours to maintain adequate levels.[159]

Dialysis should be continued until the ethylene glycol level is less than 20 mg/dl, the acidosis has resolved, and there are no signs of systemic toxicity or until the ethylene glycol level is undetectable.[147] If an ethylene glycol level cannot be quickly obtained, dialysis should be continued until the serum osmolar gap and anion gap return to normal, suggesting that ethylene glycol and glycolate levels have dropped.[5] A confirmatory ethylene glycol level should be drawn, because the normal osmolar gap suggests but does not guarantee a low ethylene glycol level.[168] Prolonged dialysis up to 8 to 10 hours may be required for very high ethylene glycol levels and severe acidosis.[143] See estimating dialysis time for alcohol intoxication addressed earlier for an example of how to approximate the necessary dialysis time. As with dialysis for methanol intoxication, these patients are prone to severe hypophosphatemia and need close monitoring of their phosphate level with replacement when indicated.[5]

TABLE 51-12 Indications for Dialysis in Patients with Ethylene Glycol Intoxication

1. Metabolic acidosis with pH < 7.25-7.3
2. Deteriorating vital signs or mental status despite supportive care
3. Renal failure
4. Refractory electrolyte imbalance
5. *Ethylene glycol > 50 mg/dl* (No longer considered an indication in certain patients—see text)

(Adapted from D.G. Barceloux, E.P. Krenzelok, K. Olson, W. Watson, American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning, Ad Hoc Committee, J. Toxicol. Clin. Toxicol. 37 [5] [1999] 537–560.)

Isopropyl Alcohol

Isopropyl alcohol or isopropanol is a colorless liquid with a bitter taste. It is used in the manufacture of acetone and glycerin. It is often used as the solvent in rubbing alcohol, and some antifreeze and windshield wiper fluid. Most rubbing alcohol contains 70% isopropanol.[5]

There were 10,016 exposures to isopropanol and no deaths reported to TESS in 2006. This represents 0.4% of all exposures reported (see Table 51-5). It has a lower associated mortality per exposure (0%) compared to methanol (0.4%) or ethylene glycol (0.6%).[1] The estimated minimum lethal dose for adults is approximately 100 ml.[169] Patients have survived ingestions of more than 1000 ml.[170]

Isopropanol reaches a peak serum level 15 to 30 minutes after ingestion. It is water soluble and has a V_d that is equal to total body water (0.6 L/kg). It has a molecular weight of 60 g/mole (see Table 51-4).[171] Isopropanol is oxidized by alcohol dehydrogenase to acetone.[172] The elimination half-life of isopropanol is 3 to 7 hours but is prolonged with ethanol coingestion.[5] The elimination of acetone is much slower and is via excretion in the breath and urine.[173]

Clinical and Laboratory Findings in Isopropyl Alcohol Intoxication

Unlike what is seen with ethylene glycol and methanol, most of the clinical effects in isopropanol intoxication are due to the parent compound.[173] Acetone causes only mild CNS depression.[173] The clinical signs of isopropanol intoxication will occur within an hour of ingestion and include effects on the CNS, GI, and cardiovascular systems (Table 51-13).[174] The CNS effects include ataxia, confusion, stupor, and coma. The GI effects include nausea, vomiting, abdominal pain, and gastritis.[174] Patients with severe intoxication can present with hypotension due to cardiac depression and vasodilatation.[38] Hypotension and coma are the strongest predictors of mortality.[174] Many patients will have fruity breath from the acetone elimination via respiration.[172]

A serum level of isopropanol equal to 60 mg/dl will increase the serum osmolarity by 10 mOsm/kg (see Table 51-3).[5] A high serum level should therefore produce a gap between the calculated serum osmolarity and that measured by freezing point depression.[5] A high anion gap acidosis is rare following isopropanol ingestion, because neither the parent compound nor its metabolites are organic acids.[174] Therefore, a finding of a high serum or urine

TABLE 51-13 Clinical Effects of Isopropyl Alcohol Intoxication

SYSTEM	CLINICAL	LABORATORY
CNS	Dizziness, ataxia, dysarthria, confusion, somnolence, coma	Ketonuria and ketonemia Osmolar gap
CV	Arrhythmia, myocardial depression, hypotension, vasodilation	Hypoglycemia Acidosis is rare and mild
GI	Abdominal pain, gastritis, nausea and vomiting	

(Adapted from J.C. Trullas, S. Aguilo, P. Castro, S. Nogue, Life-threatening isopropyl alcohol intoxication: is hemodialysis really necessary? Vet. Hum. Toxicol. 46 [5] [2004] 282–284.)
CNS, central nervous system; *CV*, cardiovascular; *GI*, gastrointestinal.

acetone level with an osmolar gap but without acidosis is suggestive of recent isopropanol ingestion.[172] Renal failure can occur in the setting of significant hypotension,[173] but the acetone can also interfere with the assay of creatinine.[175] Hypoglycemia can result from the interference of gluconeogenesis by isopropanol.[172]

Treatment of Isopropyl Alcohol Intoxication

Supportive treatment for isopropyl alcohol intoxication includes circulatory support with fluids or vasoconstrictors in patients with hypotension.[5] Inhibition of alcohol dehydrogenase is not indicated since acetone is less toxic than isopropanol.[176] Hemodialysis is indicated for patients with an isopropanol level of greater than 400 mg/dl who also have significant CNS depression, renal failure, or hypotension.[170] Hemodialysis will remove both isopropanol and acetone effectively. High efficiency membranes can produce clearance constants of greater than 200 ml/min for both acetone and isopropanol.[5]

Salicylates

There were 43,692 reported intoxications with salicylates and 16 deaths, which is approximately 2% of all exposures and 1.2% of all deaths, reported to the TESS in 2006 (see Table 51-5).[1] Salicylates are found in many commonly used medications including aspirin and aspirin-containing medications, topical lotions, and oil of wintergreen.[71] There have been reports of salicylate toxicity and in rare instances death from sports creams that contain methyl salicylate, also known as oil of wintergreen.[177] Many preparations have an enteric coating, which slows absorption to over 12 hours. Toxicity usually develops with ingestions greater than 150 mg/kg with serious toxicity in ingestions of 300 to 500 mg/kg.[178]

Pharmacokinetics of Salicylates

The most common salicylate is acetylsalicylic acid (ASA) or aspirin. ASA is converted to salicylic acid in the GI tract.[179] The absorption of both ASA and salicylic acid is usually rapid but can be delayed with enteric-coated medications and large ingestions.[180] Concretions or clumps of ASA tablets can form in large ingestions and significantly delay absorption.[180]

Salicylic acid is responsible for all of the toxic effects of ASA ingestion. The V_d depends on the amount ingested. At pharmacological doses, binding to albumin is high, which keeps the compound extracellular and the V_d low (0.2 L/kg). With overdoses, the protein binding is saturated and the V_d increases to 0.4 L/kg or greater.[179] The distribution of salicylic acid is also dependant on pH. Only the nonionized form can penetrate the cell membrane, and therefore when the systemic pH falls and more salicylate is in the form of salicylic acid, there is a greater distribution into the cells.[181] This is very important clinically since salicylate causes its major toxicity once it is intracellular.[62]

The metabolism and excretion of salicylic acid is also concentration dependent.[182] The enzymatic metabolism of salicylic acid is saturable, and at high levels, most of the removal is then due to excretion of salicylic acid in the urine.[179] The excretion of salicylate is dependent on pH as well. Alkalinization of the urine increases the ionized form of salicylate, which is then unable to diffuse out of the urine back into the tubular cell.[181]

Clinical and Laboratory Findings in Salicylate Intoxication

Table 51-14 lists the most common findings in salicylate intoxication. The symptoms of salicylate intoxication differ according to the age of the patient and whether the intoxication is acute or chronic.[183] Most people will have some clinical effect of intoxication with serum levels greater than 40 mg/dl.[179] In chronic intoxication and in the elderly, symptoms will occur at lower levels.[184] The common symptoms in all settings are nausea, vomiting, tachypnea, tinnitus, stupor, coma, and convulsions.[185] In severe intoxication, patients can develop kidney and respiratory failure, cardiovascular collapse, and coma. Prognosis is not well-correlated with serum levels and can be better estimated by the degree of hypotension, mental status changes, acidosis, and respiratory failure.[186] The more severe complications of intoxication, including respiratory failure, renal failure, seizures, coma, and death, are all more likely in the elderly and in chronic ingestions.[62] The CNS toxicity from salicylate poisoning is thought to be due to a number of factors including cerebral edema, cerebral hypoglycemia, and cerebral white matter damage.[187]

The acidosis is due to uncoupling of oxidative phosphorylation in the Krebs cycle and accumulation of lactic acid and

TABLE 51-14 Clinical Effects of Salicylate Intoxication

SYSTEM	CLINICAL	LABORATORY
CNS	Tinnitus, decreased hearing, agitation, somnolence, confusion, seizure, cerebral edema, coma	Metabolic acidosis Respiratory alkalosis Transaminitis
Pulmonary	Tachypnea, ARDS, respiratory failure	Hypoglycemia Coagulopathy
CV	Hypotension, CHF, cardiovascular collapse	
GI	Nausea, vomiting, gastritis, hepatitis	
Renal	Volume depletion, proteinuria, AKI	

(Adapted from L. Yip, R.C. Dart, P.A. Gabow, Concepts and controversies in salicylate toxicity, Emerg. Med. Clin. North Am. 12 [2] [1994] 351–364.)
AKI, acute kidney injury; *ARDS*, acute respiratory distress syndrome; *CHF*, congestive heart failure; *CNS*, central nervous system; *CV*, cardiovascular; *GI*, gastrointestinal.

ketoacids.[188] Hyperventilation occurs from direct stimulation and can lead to a respiratory alkalosis.[185] Children are more likely to demonstrate fever and severe metabolic acidosis, whereas adults are more likely to experience noncardiogenic pulmonary edema, especially those with a history of smoking.[178]

Supportive Therapy for Salicylate Intoxication

Activated charcoal is effective in reducing the gut absorption of salicylate in acute intoxication. Activated charcoal is recommended for all patients who present within 1 hour of a potentially toxic salicylate ingestion.[15] It should also be considered for patients who ingest enteric-coated preparations or who have rising serum levels, suggesting continued absorption. For these patients, repeated doses of activated charcoal may be beneficial if the level continues to rise.[30] The dose is 50 g in adults or 1 g/kg in children.[15]

As described earlier, renal excretion is very important at toxic serum salicylate levels as the enzymatic metabolism is saturable.[179] Reabsorption of salicylate in the proximal convoluted tubule depends on the urine flow rate and urine pH.[181] In an alkaline environment, salicylate is ionized. For this reason, urinary alkalinization can increase the renal clearance significantly through ion trapping.[23] Sodium bicarbonate can be used to increase serum pH and raise urine pH to greater than 7.5.[189] Many patients present with volume depletion, and the solute load will restore volume and therefore help maintain urine output as the bicarbonate helps to maintain a high urine pH.[62] See Table 51-1 for the method in urine alkalinization. Forced diuresis does not appear to increase clearance and may lead to volume overload and worsen electrolyte disturbances.[26] The use of acetazolamide should be avoided, because it can increase the risk of systemic acidosis.[62]

As described earlier, salicylate distribution to tissues and therefore toxicity is dependent on serum pH.[179] The concentration in the CNS will increase as the serum becomes more acidic.[179] This concept helps explain the importance of treatment with sodium bicarbonate or hemodialysis to correct acidosis. Patients often present with respiratory alkalosis, which helps protect the serum pH. Care must therefore be taken with any form of sedation or mechanical ventilation to maintain the respiratory alkalosis as much as possible.[190] Rapid neurological deterioration and death has been described in patients who became more acidemic in the setting of initiation of mechanical ventilation.[186] Glucose should be added to the intravenous fluids because both hypoglycemia and low CNS glucose levels without systemic hypoglycemia are common in salicylate poisoning and can worsen its CNS toxicity.[191]

Extracorporeal Therapy for Salicylate Intoxication

Salicylates have a small V_d (0.21 L/kg), a low molecular weight (138 Da), but a fairly high degree of protein binding at therapeutic levels (about 80%-90%).[49] These characteristics would suggest that hemoperfusion would be the best extracorporeal therapy for salicylate intoxication.[75] However, protein binding is saturable and declines with toxic levels to around 30% to 50%.[192] Concomitantly, the V_d increases (to ~0.35 L/kg) with toxic levels, because the unbound drug is no longer trapped in the vascular space.[179] With toxic salicylate levels, therefore, hemodialysis is as effective as hemoperfusion at removing the compound.[193] Hemodialysis is the preferred method, because of the inability of hemoperfusion to correct acid-base and electrolyte disorders and volume disturbances.[62] The correction of the acidemia can have a rapid clinical effect as pH rises and the salicylate becomes ionized and can no longer diffuse into the cells.[179]

Because serum levels correlate poorly with toxicity, the serum level should not be the major criteria for hemodialysis.[186] Hemodialysis should be considered for patients with signs of salicylate toxicity who have either a known ingestion of salicylate or a toxic serum salicylate level. Indications would include refractory acidosis, declining neurological status, seizures, ARDS or pulmonary edema, circulatory collapse, and AKI.[185] See Table 51-15 for indications of dialysis in patients with salicylate poisoning. Serum levels that would be expected to lead to this degree of toxicity are greater than 100 mg/dl in acute ingestion and as low as approximately 60 mg/dl in chronic ingestion and the elderly.[179] Because the major excretory pathway for salicylates with toxic levels is via glomerular filtration, patients with either acute or chronic kidney disease may need hemodialysis at a lesser degree of toxicity or serum level compared to patients with normal kidney function.[182] Dialysis should be continued until the following conditions are met: 1) The serum salicylate level drops to the therapeutic range; 2) resolution of acidosis; and 3) improvement in symptoms of intoxication.[62]

Lithium

Lithium has become one of the essential drugs of modern psychiatry. It is a first line medication for bipolar disorders, and it also has efficacy in the treatment of major depression. It is the only medication that has been shown to decrease the suicide risk in bipolar disorders.[194] It also has a narrow therapeutic index with toxic manifestations seen at the upper end of the effective serum concentrations for the treatment of manic episodes (0.8 to 1.5 mEq/L).[195] The increased use of lithium over the past few decades has therefore led to an increase in the number of intoxications, both accidental and as a suicide attempt. In 2006, there were 5674 toxic exposures and 7 deaths reported to TESS, which is a 0.12% mortality rate (see Table 51-5).[1] This is a five fold increase in reported lithium intoxications over the past 20

TABLE 51-15 Indications for Dialysis in Patients with Salicylate Intoxication

1. Severe toxicity with central nervous system depression, acute respiratory distress syndrome, acute kidney injury, acidemia, or coagulopathy
2. Worsening acidemia, pulmonary edema, central nervous system symptoms, or renal function despite supportive care
3. Signs of toxicity in older patients with chronic ingestion and chronic kidney disease, liver, or heart disease
4. A level > 100 mg/dl in acute ingestion or > 60 mg/dl in chronic ingestion will often meet criteria for dialysis, but a level alone is not an indication for dialysis

(Adapted from L. Yip, R.C. Dart, P.A. Gabow, Concepts and controversies in salicylate toxicity, Emerg. Med. Clin. North Am. 12 [2] [1994] 351–364.)

years.[155] The risk of toxicity increases when it is used as long-term therapy, both in acute on chronic toxicity and with toxicity due to impaired elimination.[196] Few patients sustain permanent sequelae of toxicity or require intervention with extracorporeal therapy, but the risk increases with duration of exposure, comorbidities that decrease elimination, and the actual serum lithium level.[197]

Pharmacokinetics of Lithium

Lithium is a cation and is usually administered with carbonate. It is almost completely absorbed in the stomach and proximal small intestine, with a peak serum concentration in 1 to 2 hours for regular-release preparations and 4 to 5 hours for therapeutic doses of sustained-release preparations but can increase to 3 to 4 days with toxic ingestions of sustained-release preparations.[90] It is not bound to plasma proteins and has a low molecular weight (74 Da), but its V_d is moderate (0.7 to 0.9 L/kg), slightly higher than that of total body water.[55] Since the V_d for lithium is higher than other intoxicants discussed thus far, it has a larger percentage that is intracellular.[4] Its distribution into and out of tissues is variable and dependant on tissue type, patient age, and chronicity of exposure.[90] For example, the distribution of lithium into and out of the CNS may take days, which could explain the increased toxicity with chronic exposure and the delay in neurological recovery, even with low serum lithium levels.[198] This slow distribution can result in a substantial rebound following extracorporeal therapy and leads to the recommendation to follow serum levels after therapy.[199]

Lithium elimination is almost entirely by the kidney.[200] It is freely filtered at the glomerulus, and then 80% is reabsorbed.[200] Factors that decrease glomerular filtration can increase lithium levels. The most common causes include angiotensin-converting enzyme (ACE) inhibition, angiotensin receptor blockers, NSAIDs, older age, and illness all lead to a decrease in kidney function.[201] Sixty percent of reabsorption occurs at the proximal tubule in the same process as proximal sodium reabsorption. Factors that increase proximal sodium reabsorption such as volume depletion, cirrhosis, congestive heart failure (CHF), and thiazide diuretics will also increase lithium reabsorption.[196] Lithium also has some reabsorption at the loop of Henle and distal tubule.[90] Loop diuretics and amiloride can decrease the more distal reabsorption of lithium.[202] Given its narrow therapeutic index and the number of drugs (e.g., ACE, angiotensin receptor blockers [ARBs], NSAIDs, thiazides) and conditions (e.g., volume depletion, cardiac failure, liver failure, sepsis) that influence its excretion, it is not surprising that inadvertent lithium intoxication is fairly common.[196]

Clinical and Laboratory Findings in Lithium Intoxication

The clinical findings in lithium intoxication are listed in Table 51-16. They depend more on chronicity of the ingestion and patient characteristics than on the lithium serum level. Otherwise healthy patients can have almost no toxic signs at very high lithium serum levels (i.e., > 6 mEq/L) after an acute ingestion while older patients with comorbidities such as heart, kidney, or liver disease can present with significant symptoms with chronic ingestion and a serum level at the high end of the therapeutic range (i.e., 2-3 mEq/L). Hansen and Amdisen in 1978 described a classification scheme for lithium toxicity as mild, moderate, or severe depending on clinical signs and symptoms.[4] Although they associated a serum level with these three categories, these authors and many others who followed have found little correlation between the serum levels and the severity of symptoms, especially in acute intoxication.[203] It is clear that clinical symptoms rather than serum levels correlate best with severity of intoxication.

TABLE 51-16 Clinical Effects of Lithium Toxicity

ORGAN	ACUTE POISONING	CHRONIC POISONING
Endocrine	None	Hypothyroidism
Gastrointestinal	Nausea, vomiting	Minimal
Cardiovascular	Prolonged QT interval, ST and T wave changes	Myocarditis
Heme	Leukocytosis	Aplastic anemia
Neurological		
Mild	Fine tremor, lightheadedness, weakness	Same as acute
Moderate	Apathy, drowsiness, hyperreflexia, muscle twitching, slurred speech, tinnitus	Same as acute Memory deficits, Parkinson disease
Severe	Choreoathetoid movements, clonus, coma, confusion, muscular irritability, seizures	
Neuromuscular	Myopathy, peripheral neuropathy	Same as acute
Renal	Urine concentrating defect	Chronic interstitial nephritis, nephrogenic diabetes insipidus, renal failure
Skin	None	Dermatitis, localized edema, ulcers

(Adapted from R.T. Timmer, J.M. Sands, Lithium intoxication, J. Am. Soc. Nephrol. 10 [3] [1999] 666–674.)

Lithium toxicity can be manifest in many organ systems including CNS, GI, renal, cardiovascular, endocrine, dermatological, and ocular, but the hallmark of lithium toxicity is the impact on the CNS.[196] Neurological symptoms can range from fatigue and fine tremor to spasticity, seizures, and coma.[4] These symptoms can be seen even with therapeutic levels in chronic ingestions and can persist long after serum levels are negligible.[204] Effects on the kidney are seen with both chronic use and acute toxicity. They include tubular dysfunction such as a concentrating defect leading to nephrogenic diabetes insipidus and renal tubular acidosis, AKI, and CKD.[205] The cardiovascular manifestations are more often seen in acute intoxication with high serum levels. They range from benign flattening and inversion of the T waves on the electrocardiogram to severe hypotension and cardiovascular collapse.[4] Lithium-related intraventricular conduction defects are observed only with toxic concentrations of lithium in patients with established heart disease or those taking other cardiotoxic agents.[206] Severe ventricular arrhythmias occur almost exclusively with acute

intoxications.[194] The GI associated symptoms include vomiting and profuse diarrhea with acute ingestion and nausea with vomiting in chronic ingestion.[196] Lithium is a cation and will therefore decrease the anion gap.[203]

Supportive Care for Lithium Intoxication

Supportive care for lithium intoxication includes prevention of further absorption and methods to increase enteric and renal excretion.[90] Activated charcoal is not effective in lithium intoxication.[15] Whole bowel irrigation with polyethylene glycol is the method of choice to remove unabsorbed pills and is likely to be most effective in patients that present within 1 hour of ingestion or after taking a large amount of sustained-release lithium.[13] It should also be considered in patients who have a rising serum level suggesting continued gastric absorption.[207] Sodium polystyrene sulfonate (Kayexalate) administration has been shown to bind lithium and decrease absorption in both healthy volunteers and in toxic ingestions.[208] The dehydrated patient should be given crystalloid resuscitation, but there is no data to support the use of forced diuresis or large volume saline infusion to increase elimination when the patient in not volume depleted.[209] Both techniques run the risk of causing volume overload and electrolyte disturbances. Amiloride to block distal reabsorption has not been shown to be effective in acute intoxication.[77]

Hemodialysis for Lithium Intoxication

Table 51-17 describes the indication for hemodialysis in lithium intoxication. Since serum levels are poorly correlated with the degree of toxicity, they should not be used as the primary determinant in the decision to perform hemodialysis in lithium intoxication.[196] Rather indications for hemodialysis are related to the degree of intoxication as manifested by signs and symptoms and the likelihood that endogenous clearance of lithium will allow for nontoxic levels in less than 1 to 2 days (see Table 51-17).[90] In acute intoxication, high serum levels are much less likely to cause significant morbidity, and therefore even patients with levels of greater than 4 mEq/L may have few symptoms and not require hemodialysis.[209] Case reports describe patients with acute intoxication and levels of 6 to 8 mEq/L who do well without hemodialysis.[210] However, all patients with acute ingestion and signs of severe toxicity or deterioration with supportive therapy should be given hemodialysis.[211] Almost all patients with chronic ingestion and a level of greater than 4 mEq/L will have severe toxicity and will need hemodialysis.[196] Patients with a level 2.5 to 4 mEq/L should have hemodialysis if they have severe symptoms such as neurological deterioration, hemodynamic instability, acute kidney injury, or ventricular arrhythmia.[209] Finally, patients with a serum level of less than 2.5 mEq/L but with signs of toxicity and who are likely to have continued toxic levels in 30 hours because of decreased renal clearance or prolonged GI absorption with increasing serum levels should also receive hemodialysis.[90] The decision to perform hemodialysis should be made within the first 6 to 12 hours of admission using the degree of toxicity and projection of lithium levels over time as determinants.[211]

TABLE 51-17 Indications for Dialysis in Patients with Lithium Intoxication

1. Acute ingestion with severe central nervous system toxicity or deterioration with supportive care (level ≈ 6-8 mEq/L)
2. Chronic ingestion and serum lithium > 4 mEq/L
3. Lithium level > 2.5 mEq/L and any of the following:
   a. Severe neurological symptoms
   b. Renal insufficiency
   c. Hemodynamic instability
   d. Conditions that increase renal sodium reabsorption (heart failure, cirrhosis)
   e. Chronic ingestion and moderate to severe symptoms
4. Any lithium level with one of the following:
   a. Severe symptoms
   b. Large ingestion where rising levels are anticipated or level is not felt to be below 1 mEq/L in 30 hr

(Adapted from E.J. Scharman, Methods used to decrease lithium absorption or enhance elimination, J. Toxicol. Clin. Toxicol. 35 [6] [1997] 601–608.)

Lithium is readily dialyzable because of its low molecular weight, water solubility, and lack of protein binding (see Table 51-4).[45] Although the extraction ratio of hemodialysis for lithium is high, lithium does have a moderate V_d (0.7 to 0.9 L/kg), is predominantly intracellular, and diffuses slowly across cell membranes, limiting the total amount of lithium cleared in a dialysis session.[196] Clearance constants for lithium during hemodialysis with high-flux membranes have been shown to be 150 to 200 cc/min, which corresponds to a half-life of about 3.5 to 5 hours.[77] A patient with a lithium level of 4 mEq/L would therefore require 2 half-lives or 7 hours of dialysis to bring the level to 1 mEq/L.

There continues to be some controversy regarding an endpoint for dialysis in lithium intoxication.[209] There are little data to support it, but many authors argue that patients should undergo dialysis until the serum level is less than 1 mEq/L.[196] Patients will therefore require 6 to 8 hours of hemodialysis (depending on the initial level) to bring the final concentration to less than 1 mEq/L. Serum levels should be checked at completion of dialysis to confirm adequate removal and then again at 3 to 4 hours after stopping dialysis to check for rebound.[196] Dialysis should be repeated if the level is once again greater than 1 mEq/L.[196] Alternatively, CRRT may be used as adjuvant therapy to follow initial hemodialysis in the case of significant rebound.[209] Since CRRT has significantly slower lithium clearances than hemodialysis, it should not be used as initial therapy unless the patient will not be able to tolerate conventional hemodialysis or high volume CRRT is used.[212] Neurological improvement may lag behind improvement in serum lithium levels, cardiac toxicity, or GI symptoms because of the slow equilibration of lithium from brain to blood.[213]

Theophylline

Theophylline is a methylxanthine bronchodilator used for obstructive airway disease. Although the number of patients using it and therefore the number of toxic exposures are declining, toxic exposure to theophylline continues to have a relatively high morbidity and mortality (see Table 51-5). In 2006, there were 413 theophylline exposures and one death reported to TESS.[1] Ten years ago there were 8 times that number of exposures.[214]

Pharmacokinetics of Theophylline

Theophylline is rapidly absorbed from the GI tract and reaches a peak serum level in 1 to 3 hours, but will peak hours or days after a large ingestion of a sustained-release preparation.[215] It undergoes hepatic metabolism by the P-450 (CYP) 1A2 system and its half-life will therefore be increased by liver disease, heart failure, a high dose, age and use of medications that inhibit P-450 enzymes such as fluconazole, cimetidine, ciprofloxacin or erythromycin.[215] The half-life will be decreased by inducers of the P-450 enzymes such as smoking, phenobarbital, and rifampin.[215] Theophylline has a V_d 0.5 L/kg and is 60% protein bound.[59]

Clinical and Laboratory Findings in Theophylline Intoxication

Signs of theophylline intoxication are listed in Table 51-18 and depend on age, chronicity of ingestion, and serum level. Signs of mild theophylline toxicity are nausea, vomiting, abdominal pain, tachycardia, and muscle tremor and are usually seen with levels of about 20 to 25 mg/L.[216] Severe toxicity consists of cardiac arrhythmias including premature ventricular contractions and ventricular tachycardia, hypotension, impaired consciousness, seizures, cardiorespiratory arrest, and ultimately death.[217] The risk of severe toxicity increases with increasing serum levels, but older patients and patients who have an acute ingestion complicating chronic use will have a much higher risk of toxicity for the same serum level.[218]

Supportive Care for Theophylline Intoxication

Supportive care for theophylline intoxication includes prevention of further absorption, interruption of enterohepatic circulation, and treatment of complications including arrhythmias and seizures.[219] Activated charcoal can bind theophylline in the GI tract and should be used initially in intoxication.[30] If the patient presents within 1 hour of acute ingestion or after ingesting a large dose of sustained-release preparation, whole bowel irrigation should be considered.[11] It is not as effective as activated charcoal and its use should be avoided if it is going to significantly delay the use of charcoal to enhance elimination.[13] Because theophylline undergoes enterohepatic circulation, MDAC may increase elimination by removing theophylline from this circulation.[220]

TABLE 51-18 Clinical Effects of Theophylline Intoxication

SYSTEM	CLINICAL	LABORATORY
CNS	Agitation, hyperreflexia, tremor, ataxia, seizures	Hypercalcemia Hypokalemia
GI	Nausea, vomiting, diarrhea, abdominal pain, hematemesis	Metabolic acidosis with respiratory alkalosis
CV	Sinus tachycardia, hypotension, volume depletion, supraventricular tachycardia, ventricular tachycardia, cardiac arrest	
Pulmonary	Tachypnea	

(Adapted from A.H. Dawson, I.M. Whyte, The assessment and treatment of theophylline poisoning, Med. J. Aust. 151 [11–12] [1989] 689–693.)
CNS, central nervous system; *CV,* cardiovascular; *GI,* gastrointestinal.

Repeated doses of activated charcoal may be given with a dose of 20 g every 2 hours in adults for 6 to 12 hours, depending on the serum theophylline level.[219] Patients with seizures will usually respond to benzodiazepines.[221] Phenytoin or phenobarbital can be used to treat refractory seizures.[222] Patients with ventricular arrhythmias will benefit from beta blockade.[223]

Enhancement of Elimination with Extracorporeal Therapies

Because of the high degree of protein binding, hemodialysis for theophylline intoxication will result in a plasma ER close to 0.5 with clearance rates approximately 100 cc/min.[224] Since theophylline's volume of distribution is fairly low, this corresponds to a half-life of 3 to 4 hours. Hemoperfusion is more effective than hemodialysis, achieving an ER of 0.6 to 0.9.[225] Hemoperfusion should therefore be considered as first line therapy, but hemodialysis should be performed where extracorporeal therapy is indicated but hemoperfusion is not available.[224]

As was seen with other intoxications such as lithium and salicylate, the indications for extracorporeal therapy depends more on the clinical setting than the absolute serum level.[215] Patients should receive extracorporeal therapy if they have cardiac instability or arrhythmias or have refractory seizures despite supportive care. In most cases this corresponds to a serum level greater than 80 to 100 mg/L in acute ingestion or greater than 60 mg/L in chronic ingestion.[222] It should also be considered for patients who have symptoms of toxicity and are older than 60 years of age and have either heart or liver disease.[226] Finally, extracorporeal therapy should be considered for patients with toxicity and increasing levels despite activated charcoal treatment (Table 51-19).[215] Hemoperfusion or hemodialysis should be continued until symptoms improve and serum drug levels are less than 15 mg/L.

DRUGS WITH HIGH PROTEIN BINDING

Drugs that have high protein binding are less likely to be effectively removed with hemodialysis.[47] For some of these drugs, hemoperfusion may be more efficacious in intoxication, but with the advent of high-flux hemodialysis, the superiority of hemoperfusion for these agents is lessened.[227] Some of these agents are discussed below.

TABLE 51-19 Indications for Hemoperfusion or Dialysis in Patients with Theophylline Intoxication

1. Severe toxicity with cardiac instability, refractory arrhythmias, or persistent seizures despite supportive care
   a. Usually seen with a serum level > 80-100 mg/L in acute intoxication
   b. Usually seen with a serum level > 60 mg/L in chronic ingestion
2. Patients with symptoms of toxicity are older than 60 years of age, have heart or liver disease and a serum level > 40 mg/L
3. Patients with symptoms of toxicity and an increasing serum level despite therapy with activated charcoal

(Data from P. Shechter, H. Berkenstat, E. Segal, J. Rapoport, Theophylline intoxication: clinical features and pharmacokinetics during treatment with charcoal hemoperfusion, Isr. J. Med. Sci. 32 [9] [1996] 766–770.)

Phenytoin

Phenytoin is a hydantoin derivate and is used to control generalized tonic clonic and complex partial seizures.[228] The V_d is 0.5 to 0.8 L/kg but will increase somewhat with a large ingestion or liver or renal disease.[229] It is highly protein bound at 90% with therapeutic levels.[230] Protein binding does decrease with a toxic ingestion, older age, or liver or renal disease.[229] Most of the toxicity related to high phenytoin concentrations is neurological, and can include nystagmus, ataxia, dysarthria, seizures, and rarely, coma.[228] Hypotension and cardiac arrhythmias can be seen with intravenous phenytoin but are rarely seen with oral ingestion.[228]

Initial treatment of a toxic ingestion of phenytoin should include methods to decrease absorption.[228] Procedures found to be most effective include oral activated charcoal for patients who present within 2 hours of ingestion and whole-bowel irrigation for patients who ingest large amounts of sustained-release tablets or whose levels continue to rise over the first 24 hours following ingestion.[15] Patients with seizures should be given benzodiazepines, and a search for other causes of seizures (e.g., coingestion of an agent that lowers the seizure threshold) should be performed.[228]

The elimination half-life of phenytoin can be reduced with MDAC, hemoperfusion, or hemodialysis.[229] MDAC should be considered in patients with a life-threatening ingestion, especially if hemoperfusion and hemodialysis are not available.[30] Hemoperfusion has been shown to be effective in the removal of phenytoin with a half-life of 4 hours.[231] Hemodialysis may not be as effective because of the high degree of protein binding but with toxic ingestion, critical illness and chronic kidney disease protein binding diminishes.[229] Hemodialysis should therefore be considered where hemoperfusion is not available, especially in patients with very high levels, CKD, or a low serum albumin.[229]

Carbamazepine

Carbamazepine is an anticonvulsant that is used to control generalized tonic clonic and complex partial seizures. It is also acts as a mood stabilizer in bipolar disorder. There has been an increase in use for other disorders such as trigeminal neuralgia, schizophrenia and attention deficit hyperactivity disorder. Carbamazepine intoxication can lead to a life-threatening array of complications. Signs and symptoms include somnolence, seizures, ataxia, respiratory depression, decreased cardiac contractility, pulmonary edema, hypotension, and acute kidney injury.[232] The V_d of carbamazepine is 0.6 to 1.2 L/kg, and as with phenytoin, it will increase somewhat with a large ingestion or liver or renal disease.[232] It is highly protein bound at 75% with therapeutic levels but the protein binding decreases with a toxic ingestion, older age, or liver or renal disease.[232] Carbamazepine excretion is via the kidney, and the half-life will be significantly prolonged in CKD or AKI.[233]

Initial treatment of a toxic ingestion of carbamazepine is similar to phenytoin and includes oral activated charcoal and whole bowel irrigation where appropriate.[15] Patients should have cardiac monitoring because of the risk of cardiac toxicity.[234] MDAC has been shown to be effective and should be considered in patients who have a life-threatening ingestion.[30] Although hemoperfusion has been considered the mainstay of therapy to enhance elimination of carbamazepine, there is increasing evidence that hemodialysis may be almost as effective in patients with severe toxicity because of the decreased protein binding with toxic levels and the increasing use of high-flux membranes.[235] Hemoperfusion or hemodialysis should be considered in patients with a deteriorating clinical status, refractory seizures, or cardiac instability.[236]

Valproic Acid

Valproic Acid is another anticonvulsant and mood stabilizer used in epilepsy and bipolar disorder. It has also been used to some effect in major depression. Intoxication with valproic acid can cause hemodynamic instability, cerebral edema, coma, hyperammonemia, and bone marrow suppression.[237] The V_d of valproic acid is 0.2 L/kg but will increase with toxic ingestion.[238] It is highly protein bound at 95% with therapeutic levels, but the protein binding decreases with a toxic ingestion, older age, or liver or renal disease and has been shown to be as low as 30% in severe toxic ingestions.[239] Treatment considerations are similar to carbamazepine and include activated charcoal or whole-bowel irrigation initially and MDAC, hemoperfusion, or hemodialysis to enhance elimination in severe intoxication.[240] Indications for hemoperfusion or hemodialysis include cardiac instability, hypotension, clinical deterioration, and hyperammonemia.[237]

Phenobarbital

Phenobarbital is a long acting barbiturate that is used for generalized tonic-clonic and partial seizures.[241] Toxicity can lead to ataxia, respiratory depression, coma, and less commonly cardiovascular collapse.[241] Oral activated charcoal is effective in decreasing absorption, and MDAC has been shown to enhance elimination by interrupting enteroenteric circulation.[242] Urine alkalinization is also effective to enhance elimination.[23] The V_d is 0.9 L/kg, and the protein binding is 50%.[241] Both hemodialysis and hemoperfusion have been shown to be effective in decreasing elimination half-life of phenobarbital.[243] These procedures should be reserved for patients with cardiac instability due to intoxication.[241]

A full list of references are available at www.expertconsult.com.

INDEX

Note: Page numbers followed by *b* indicate boxes, *f* indicate figures and *t* indicate tables.

D

J

K

L

N

O

Q

R