INFECTIOUS DISEASES IN OBSTETRICS AND GYNECOLOGY

FIFTH EDITION

GILLES R. G. MONIF, MD
AND
DAVID A. BAKER, MD

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Preface

To the Fifth Edition

The challenge of each new edition has been to innovate without altering an unstated mandate to deliver sophisticated information in a pragmatic form so as to better empower and educate those who man the patientphysician frontier.

Those authors who contributed to the book were chosen because of their extensive clinical experience as well as intellect which enables them to supersede the printed word when it errs.

Editorially, I am pleased to exposed the readers to the talents of David Baker and Mark Martens.

Dedication to the Fifth Edition

Without art there can be no true science and without a love of humanity there can be no true art. This edition is dedicated to those who help forge and nurture these concepts and we hope this work will enhance the quality of care rendered to women.

Part I
General Considerations

1
Understanding the bacteriology of the female genital tract

Compared to our understanding of bacterial diseases of the female genital tract, relatively little is understood about what constitutes and maintains a healthy ecological system within the microbiological flora of the female genital tract. Why is an understanding of normality important? At some future date, therapy may graduate from the eradication of pathogen bacteria causing disease to promotion of bacteria responsible for vaginal/cervical microbial wellness, and physicians may prevent disease rather than eradicate it through the use of probiotics.

That one microbial species can inhibit a different form of microbe has resulted in the coining of the term ‘probiotics’. A probiotic is the feeding or placing of an organism or product which enhances or maintains a nonpathogenic flora. Gorbach’s advice as to what constitutes a probiotic is important to understand that less noneffiacious combinations of organisms or products destroy the perceived validity of the approach of competitive inhibition of pathogenic or potentially pathogenic bacteria…“the purported benefits for any probiotic must pass the highest standard of scientific scrutiny before the claims can be accepted”.

The shallowness of our microbiological observations emanate from the inadequacy of sampling technology, failure to quantitate the majority of observations and the seeming lack of it’s importance.

Analysis of published studies reveals compromising of microbiological data by inappropriate or suboptimal methods of culturing, failure to use appropriate transport media or enriched media and/or a lack of stringent adherence or use of anaerobic technology in the processing and culture of specimens.

The isolation of a given bacteria does not necessarily confer significance as to its functional significance. The microbial load of a given bacteria appears to govern the relative risk of asymptomatic versus symptomatic infection. Case in point is *Streptococcus pneumoniae*. During the winter months, it is not uncommon for 4–5% of the population to have nasal colonization with an encapsulated strain of the bacteria, unassociated with disease. Quantitative studies document the relatively low level of bacterial replication. In contrast, pneumococcal disease is associated with a five to six log increase in demonstrable organisms. Louis Pasteur put this concept into clear perspective when he asserted that “the mere presence of an organism is insufficient to produce disease”. What constitutes a pathogen in a given situation is not only the type of offending organism and its specific virulence, but also the absence of competitive microbial governance.

Insufficient attention in the study of bacterial disease has been given, not to which bacteria is isolated, but rather what bacteria which are normal inhabitants of a given focus of disease are not present. Bacteria causing overt streptococcal disease, whether it be of the upper respiratory tract or the female genital tract, have few, if any co-isolates. Similarly in acute disease due to groups A and B streptococci, with the exception of *Staphylococcus aureus* and *epidermidis*, few or any other normal flora bacteria are concomitantly isolated.

Table 1.1 Prevalence of aerobic (facultative) isolates reported in vaginal flora studies in the published literature

Aerobic isolate	***Prevalence in vaginal flora (%)***		
	Low	***Mean***	***High***
Gram-positive rods			
Diphtheroids	3	40	80
Lactobacilli	18	60	90
Gram-positive cocci			
Staphylococcus aureus	0	2	25
Staphylococcus epidermidis	5	50	95
Streptococcus species			
alpha-hemolytic	8	20	38
beta-hemolytic	3	15	22
Nonhemolytic	0	20	32
Group D	2	28	45
Gram-negative rods			
Eschehchia coli	3	18	33
Klebsiella and *Enterobacter* species	0	10	20
Proteus species	0	5	10
Pseudomonas species	0	0.1	3

From Larsen B. Microbiology of the female genital tract. In: Pastorck J, ed. *Obstetric and Gynecologic Infectious Disease*. New York: Raven Press, 1994:11–25

BACTERIOLOGY OF NORMAL FEMALE GENITAL TRACT FLORA

The microbiological flora of the normal female genital tract constitutes a dynamic interplay of microbial and environmental checks and balances.

Disease of the female genital tract can be due to endogenous bacteria such as *Bacteroides/Prevotella* species, *Gardnerella vaginalis* or the group B streptococcus or exogenous bacteria such as *Neisseria gonorrhoeae* or the group A streptococcus.

In order to understand abnormality, one must first understand normality: what bacteria are considered the normal inhabitants of the female genital tract.

The number of bacteria recoverable from the lower female genital tract is relatively staggering. The aerobic isolates and their relative prevalence is listed in Table 1.1; that for anaerobic bacteria is designated in Table 1.2. The divergences of isolates from one woman to another is not a phenomenon of randomness. When quantitative and inhibition studies are done, a picture of a highly regulated governance is demonstrable.

Once the normal bacterial constituents of the female genital tract are defined, one is confronted with having to explain why apparently commensal bacteria, such as *G. vaginalis*, group B streptococcus and *Escherichia coli*, are transformed into regional pathogens and produce disease.

Change in the local microbiological environment is one of the principal means by which endogenous bacteria gain the numerical representation necessary for suppression of competitive bacterial inhibitors and production of disease or introduction of environmental factors which directly stimulate specific bacteria: quantitative replication. In animal model systems, peritonitis is more frequently induced when blood is injected with the threshold inoculum. Myonecrosis occurs when calcium chloride is implanted into the muscle along with the *Clostridium* species. Salmonellosis can be induced in animals by the administration of an antibiotic which eradicates its competitive inhibitors.

For endogenous bacteria which gain access to the female genital tract, such as *N. gonorrhoeae* or group A streptococcus, an alteration of a natural host defense barrier needs to occur. The most common factor is the loss of mucosal integrity, blood alteration of local pH and mechanical compromise of endocervical mucus. Virulence is constitutive to a given pathogen. The number of organisms in the linear phase of growth determine the amount of enzyme, exotoxin, endotoxin, etc. available for disease production.

Table 1.2 Prevalence of anerobic microorganisms present in cultures of cervical and vaginal specimens obtained from asymptomatic women (selected reports)

Organism	***Percentage according to reference***				
	A	***B***	***C***	***D***	***E***
Bacteroides species					
B. bivius[1]	-	21	-	-	-
B. fragilis	17	4	40	12	16
B. melaninogenicus[2]	-	-	-	33	-
Other	40	-	18	46	-
Bifidobacterium species	10	-	-	2	2
Clostridium species					
C. perfringens	3	4	-	-	-
Other	13	2	-	-	-
Any	-	-	-	4	0
Eubacterium species	3	7	-	31	7
Fusobacterium species	-	7	28	13	-
Gaffkya species[3]	-	-	-	2	-
Lactobacillus species	-	10	-	46	52
Peptococcus species[4]					
P. asaccharolyticus	-	48	-	12	-
P. magnus	-	11	-	17	-
P. prevotii	-	17	-	21	-
Other	-	11	-	33	-
Any	7	-	64	65	8
Peptostreptococcus species					
P. anaerobius	-	34	-	15	-
P. intermedius	-	5	-	10	-
P. micros	-	7	-	8	-
P. productus	-	-	-	6	-
Any	33	-	76	35	15
Propionibacterium species	-	2	-	8	0

Veillonella species	27	11	6	4	0

Dashes signify no specific information available.
[1]*Prevotella bivia,* [2]*Prevotella melaninogenicus,* [3]*Aerococaus species,* [4]*Peptostreptococcus species*
A: Keith LG, England D, Barizal F, *et al.* Microbial flora of the external os of the premenopausal cervix. *Br J Vener Dis* 1972; 48:51
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Adapted with permission from Larsen and Monif. *Clin Infect Dis* 2001; 32:69

WHAT DISEASE HAS TAUGHT US

Studies of bacterial diseases within Obstetrics and Gynecology have demonstrate several key principles:

(1) monoetiological bacteria produce disease by numerical expansion;
(2) aerobic virulent bacteria can alter disease spectrum by the recruitment of additional bacteria;
(3) anaerobic bacteria require a low oxidation-reduction potential to allow a single anaerobic bacteria to progress to abscess formation;
(4) anaerobic bacteria can utilize more aerophilic bacteria to collectively produce disease and;
(5) changes within the locus of disease can cause autoelimination of inciting and/or contributing organisms.

Monoetiological pathogens

Monoetiological bacteria are bacteria whose genetic virulence is capable of producing disease without intervention of other bacteria or significant alteration of oxidation-reduction potential. Both exogenous bacteria, i.e. group A streptococci, and endogenous bacteria, i.e. *E. coli,* can do so. What is required is a breach of anatomical barriers to bacterial invasion such as parturition. In these situations, the bacteria attain access to a site in which no bacteria capable of its inhibition exist in large numbers.

Other monoetiological pathogens require a release from the inhibitory effects of the dominant bacteria locally functioning: prime aerobic example, *Salmonella typhi,* prime anaerobic bacteria, *Clostridium difficile.* In both cases, antibiotics with significant spectrum of efficacy for Gram-positive anaerobic bacteria release the bacteria from their local inhibitory restraints. Their numerical increase, in the case of *Salmonella typhi,* exceeds the threshold inoculum, and in the case of *C. difficile* for exotoxin production necessary for disease induction.

Synergistic coupling

Within obstetrical and gynecological bacterial infections, the best example of synergistic coupling is progressive synergistic bacterial gangrene in which *Staphylococcus aureus* combines with a micro-aerophilic streptococcus to produce a disease that neither organism can cause independently.

Immediate anaerobic syndrome

Contamination of a hematoma with a single class III anaerobic bacteria and its subsequent conversion into an abscess is the classical example of the immediate anaerobic syndrome. This syndrome occurs when a low oxidation-reduction potential is combined with a bacteria capable of successful replication under such conditions.

The anaerobic progression

The anaerobic progression occurs when the environment with a contiguous bacterial flora lowers its oxidation-reduction potential, but does not lower it sufficiently to permit the immediate anaerobic syndrome. Initial replication by aerobic/microaerophilic bacteria within the contiguous flora further lowers the oxidation-reduction potential. In so doing, they promote the growth of more anaerobic bacteria which in turn begin the process of autoelimination of the then governing bacteria. Within the anaerobic progression, both selective recruitment and autoelimination occur. The classical example of the anaerobic progression is gonococcal salpingitis in which *N. gonorrhoeae* initiates the first phase of disease and then recruits mixed aerobic/anaerobic bacteria which result in tissue damage as well as ultimate elimination of *N. gonorrhoeae*. In a sense, the anaerobic progression cures an individual of the gonococcal infection, but usually at the price of tissue destruction.

MICROBIAL REGULATORS OF VAGINAL BACTERIAL FLORA

Bacteria reside within the female genital tract by virtue of systems of checks and balances. Anything which disturbs a governing component will realign the distribution and quantitative distribution of the bacteria present.

Bacteria have the ability to inhibit one another. They do so through the elaboration of a number of antimicrobial by-products, i.e. bacterocins, hydrogen peroxide, hemolysins, etc. The effectiveness of the resultant inhibitory substance is a function of bacterial susceptibility to it, its potency and the number of producing organisms.

Only two bacteria, *Lactobacillus* species and *G. vaginalis* have been shown to be recoverable as sole isolate from the female genital tract. What is implied by this fact is that they can individually function as ultimate regulators of the bacterial flora of the female genital tract. The term applied to the ability of one bacteria to suppress replication of another is called ‘bacterial interference’. *In vitro* studies of Chaisilwattana and Monif have documented the ability of *Lactobacillus* species to inhibit *G. vaginalis*, and conversely, the ability of *G. vaginalis* to inhibit *Lactobacillus* species. Quantitative relationship between these two bacteria is the key to which will govern the bacterial flora.

The ability of each to impose bacterial interference on the other when present in high multiplicity has been shown in clinical studies. Carson *et al.* identified *Lactobacillus* species in 131 cultures of vaginal specimens. *G. vaginalis* was recovered as a co-isolate in only seven cases. In six of the seven cases, the multiplicity of co-isolates implied that both organisms existed in low multiplicity within the anaerobic progression. When women with bacterial vaginosis in which *G. vaginalis* isolates predominated at high multiplicity, aerobic *Lactobacillus* species were never isolated.

The absence of aerobic *Lactobacillus* species is a marker of a bacterial flora at risk for tendency towards becoming an abnormal bacterial flora with polybacterial and significant anaerobic bacterial representation. Microbiological environment can supercede virulence in the production of disease. For disease to occur, exogenous and endogenous bacteria must possess pathogenic prerequisites and attain replicative dominance. Their ability to do so is largely governed by inhibitory or synergistic interrelationships with other bacteria.

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2
Immunological defense mechanisms in the female genital tract

Steven S.Witkin, PhD

The lower portion of the female genital tract is exposed to numerous microorganisms from environmental contact, contamination from the rectum and fingers, during sexual activity, soiled underclothing, etc. In addition, colonization of the vagina with potentially pathogenic microorganisms is universal. Immune defense mechanisms have evolved to protect women from developing clinical infections as a result of this microbial onslaught. Until recently, studies of female genital tract immunity were limited for the most part to a description of antibody concentrations and isotypes. In the past several years, however, spurred in part by the need to understand factors involved in the heterosexual transmission of the human immunodeficiency virus (HIV) there has been a concerted interest in other female genital tract immune defense mechanisms. The participation of female genital tract epithelial cells in immune defense has also been verified.

The immune system can be subdivided into innate and acquired immunity. Innate immunity is rapid, nonspecific and involves a very limited number of genes (probably <100). It is the initial response to infection and alerts the acquired immune system to the need to initiate a pathogen-specific antibody and/or a cell-mediated immune response. Acquired immunity, in contrast, takes several days to develop, is induced in response to a specific microbe and recognizes only that microorganism and involves a great number of genes (approximately 10^{15}).

INNATE IMMUNITY

A major component of the innate immune system is the toll-like receptors (TLRs) present on the surface of antigen-presenting cells such as macrophages and dendritic cells as well as on epithelial cells. First identified in *Drosophila* and later in mammals including man, the TLRs recognize specific molecules on microbial pathogens called pattern-associated molecular patterns (PAMPs). For example, TLR2 recognizes yeast zymosan, bacterial lipoproteins and peptidoglycan from Gram-positive bacteria. TLR4 recognizes lipopolysaccharide from Gram-negative bacteria, TLR5 recognizes bacterial flagellen while TLR9 recognizes a unique dinucleotide sequence, unmethylated CpG, only present in bacterial DNA. The binding of a specific microbial component to a TLR activates the intracellular pathway leading to transcription of pro-inflammatory cytokines, activation of phagocytic cells and the triggering of cell-mediated immunity.

An additional mechanism of innate immune system activation of adaptive immunity is provided by the heat shock proteins. Heat shock proteins, also first identified in

Drosophila, were named because their intracellular concentration greatly increased when cells were exposed to elevated temperatures. It later became apparent that any cellular stress including exposure to infectious agents resulted in a rapid activation of several heat shock protein genes. Under the so-called 'danger hypothesis', the release of heat shock proteins from damaged stressed cells is the initial signal to the immune system that danger is present and immune activation is required. Several different heat shock proteins bind to receptors on antigen presenting cells, triggering their maturation and the release of pro-inflammatory cytokines that activate T and B lymphocytes. One member of the heat shock protein family, the 70kDa heat shock protein, has also been shown to directly activate the complement system. This provides another antigen-nonspecific mechanism of combating microbial invaders. Activated complement components are capable of lysing bacterial cells and, by depositing complement component C3 on the bacterial surface, marking these cells for ingestion by phagocytic cells that contain cell surface C3 receptors.

Antimicrobial peptides are also components of innate immunity. They are expressed by phagocytic and epithelial cells and are capable of disrupting the cell membranes of a broad spectrum of Gram-positive and Gram-negative bacteria, fungi and enveloped viruses. Under physiological conditions these peptides have a cationic charge and so bind to anionic moieties on the microbial surface. The most widely studied antimicrobial peptides are the defensins, six of which have been identified in man. Additional antimicrobial peptides in man include human cationic antimicrobial protein-18 (hCAP18), histatins, lipophilins and NK lysine.

Another innate inhibitor of viruses, bacteria and fungi is called secretory leukocyte protease inhibitor (SLPI). This protein is a serine protease inhibitor produced by epithelial cells and present in many body secretions. A recent study has suggested that SLPI blocks the binding of HIV to target cells, thereby inhibiting its transmission.

ACQUIRED IMMUNITY

In contrast to innate immunity that is a generalized and nonspecific immune response to infection, acquired immunity is specific for the particular pathogen that is present. Briefly, antigen presenting cells such as macrophages and dendritic cells engulf the pathogen or pathogen components and break them down into small peptides. The peptides then associate with molecules belonging to either class 1 or class 2 of the major histocompatibility complex (MHC) and the peptide-MHC complexes are transported to the cell surface. T helper lymphocytes as well as B lymphocytes have receptors that recognize peptide-MHC complexes on antigen presenting cells. When a single T cell binds to the microbial peptide-MHC complex the cell 'learns' to recognize that specific microbial antigen. The activated T cell than releases the cytokine interleukin(IL)-2 which initiates its rapid multiplication resulting in a population of antigen specific cells. The T cells activate B lymphocytes which then also bind to processed antigens. The resulting proliferation of these antigen-specific B cells results in the formation of an antibody producing army with specificity for this one microbial antigen. The T cells also release interferon gamma (IFN-gamma) which activates phagocytic cells to more effectively engulf and process microbes and so create additional T and B cells with specificity for

other micro bial antigens. The net result is the formation of so-called memory T and B cells capable of activating an antibody or cell-mediated immune response whenever in the future that specific microbial antigen is recognized.

VAGINAL EPITHELIAL CELLS AND INNATE IMMUNE DEFENSE MECHANISMS

It has become increasingly clear that epithelial cells in the vagina contribute to the local immune defense against microbial pathogens. The vaginal mucosa does not contain many immunocompetent cells and so the vaginal epithelium is the first line of defense against exogenous microbial pathogens. Vaginal epithelial cells, as well as epithelial cells in the ectocervix and endocervix, have recently been shown to express several TLRs: TLR1, TLR2, TLR3, TLR5 and TLR6. TLR4 was conspicuously absent. The capacity of TLRs to recognize the presence of diverse microbial pathogens bestows on the vaginal epithelium the function of sentinel. A microbial invader binds to the TLRs and triggers the epithelial cells to synthesize and release pro-inflammatory cytokines. This, in turn, summons and activates cells of the acquired immune system to mount a specific immune attack. The cytokines IL-1, 6, 8, 10, 12, tumor necrosis factor alpha (TNF-alpha) and macrophage colony stimulating factor have all been detected in vaginal fluids and/or in vaginal epithelial cell culture supernatants. In addition, IFN-gamma and TNF-alpha have been shown to induce the expression of MHC class 2 antigens on vaginal and cervical epithelial cells *in vitro*. This converts these cells into antigen presenting cells, enabling them to present microbial antigens for recognition by T lymphocytes.

SLPI has been identified in the female genital tract and is produced by epithelial cells in the vagina. The ability of SLPI to inhibit microbial growth has already been mentioned. Women with lower genital tract infections such as *Trichomonas vaginalis, Neisseria gonorrhoeae, Chlamydia trachomatis* and *Candida albicans* and with disturbed vaginal flora characteristic of bacterial vaginosis have reduced levels of SLPI in the vagina. Microbe-produced proteases probably degrade SLPI and, thereby, aid the proliferation of these microorganisms. It has been hypothesized that one mechanism whereby vaginal infections function as co-factors for the sexual transmission of HIV is by degradation of SLPI, an inhibitor of HIV binding to target cells.

At least three antimicrobial peptides, beta-defensin-1 and intestinal defensin-5 as well as hCAP18, have been shown to be expressed by the vaginal epithelial cells. Beta-defensin-1 levels are highest in pregnant women indicating a hormonal influence on its expression. Similarly, defensin-5 reaches its highest concentration in the vagina during the secretory phase of the menstrual cycle. Synthesis of both defensin-5 and hCAP18 are up-regulated by pro-inflammatory cytokines suggesting their role in combating infection in the vagina.

Additional components of innate defense produced by vaginal epithelial cells include the antimicrobial compounds lactoferrin and lysozyme.

ANTIBODY PRODUCTION IN THE FEMALE GENITAL TRACT

The female genital tract is a component of the mucosal immune system, which is distinct from circulating immunity. Most of the antibodies present in the female genital tract are produced locally and differ in specificity from antibodies present in the blood. Thus, it is possible for women to have antibodies to a genital pathogen in her cervico-vaginal secretions while these antibodies are absent from her serum. This point has clinical implications for antibody testing. For example, in women undergoing *in vitro* fertilization (IVF) the presence of antibodies to *C. trachomatis* in cervico-vaginal fluids correlates with a poor IVF outcome. In contrast, there is no relation between circulating anti-chlamydial antibodies and IVF success.

Most of the antibody-producing cells in the female genital tract are located in the endocervix, although antibody-producing cells have also been identified in the ectocervix and the vagina. Polymeric secretory IgA is the major immunoglobulin produced within the genital tract. IgG antibodies are also present in genital tract secretions and probably consist of a mixture of locally produced antibodies and systemic antibodies that enter the genital tract by transduction in the vagina and the uterus. The concentrations of antibodies produced in the cervix varies throughout the menstrual cycle. Antibody levels are highest during menstruation and lowest during the periovulatory period.

A major question that has been brought into sharp focus by the acquired immunodeficiency syndrome (AIDS) epidemic is how to optimally induce local female genital tract immunity as distinct from systemic immunity. Surprisingly, it has recently been demonstrated that the induction of immunity within the nasal cavity appears to be the most effective means for inducing long lasting immunity in the female genital tract to a wide variety of antigens. By mechanisms still to be delineated activated antigen presenting cells and T and B lymphocytes in the nasal mucosa apparently preferentially migrate to the mucosa of the female genital tract.

RECURRENT VULVOVAGINAL CANDIDIASIS: AN IMMUNE DISORDER

In most women the presence of *C. albicans* in the vagina leads to the release of cytokines that activate phagocytic cells to engulf and destroy this microorganism. In addition, production of IFN-gamma inhibits the yeast form of *C. albicans* from germinating into the invasive fungal phenotype. Thus, the immune response to *C. albicans* prevents its proliferation to levels capable of causing clinical symptoms. It can be readily appreciated that interference with pro-inflammatory cytokine production would leave the individual highly susceptible to developing a clinical *C. albicans* infection, provided of course that subclinical levels of this microorganism are already present. This is precisely what occurs in many women suffering from recurrent vulvovaginal candidiasis.

One mechanism leading to the inhibition of pro-inflammatory cytokine production is an allergic (immediate hypersensitivity) response. If a woman is allergic to a compound (allergen) she has IgE antibodies that are bound to the surface of basophils and mast cells

which recognize this specific allergen. When exposure to the allergen occurs the allergen binds to these IgE antibodies, triggering the basophils and mast cells to release histamine as well as other inflammatory media-tors. The histamine induces macrophages to release high concentrations of prostaglandin E_2 (PGE_2) which inhibits the release of pro-inflammatory cytokines and blocks phagocytic cell activation. Furthermore, other cytokines, notably IL-4, IL-5, IL-6 and IL-10, are induced under these conditions that stimulate further production of IgE antibodies.

The induction of allergic responses in the human vagina has been amply demonstrated. Allergens shown to induce a vaginal allergic response include seminal fluid constituents, *C. albicans*, environmental allergens such as rye grass and pollen, and components of contraceptive spermicides or antifungal medications. The seminal fluid allergen in some cases is an intrinsic component present in all seminal fluids. In other cases it might be an allergen unique to one particular seminal fluid: a medication or food ingested by the male and present in the ejaculate. It is also possible for a male with a genital allergy to transmit both IgE antibodies and allergen to the female during sexual intercourse, resulting in induction of a vaginal allergic response in a non-allergic woman.

C. albicans has several unique properties which enable it to take advantage of localized allergic reactions. This microorganism is able to synergize with histamine to greatly increase the concentration of PGE_2 released by macrophages. Furthermore, PGE_2 stimulates the yeast to hyphae morphogenetic transition of *C. albicans,* increasing its pathogenicity Recent studies have demonstrated that *C. albicans* possesses an immunosuppressive PGE_2-like molecule which also induces hyphae formation.

C. albicans is present in the vagina of about 20% of women as a commensal microorganism. If a vaginal allergic reaction occurs in a woman harboring this microorganism, the resulting localized immune responses will allow the *Candida* to proliferate and to undergo a transition to the hyphae form. This will result in the clinical symptoms characteristic of vulvovaginal candidiasis. Subsequent antifungal antibiotic treatment will most likely result in an alleviation of symptoms. However, since all current antifungal drugs are fungistatic and not fungicidal low levels of *Candida* will remain in the vagina. This will leave the woman susceptible to recurrent vulvovaginal candidal infections upon subsequent exposures to an allergen to which she is sensitized. It has been demonstrated using the highly sensitive polymerase chain reaction that women with a history of recurrent vulvovaginal candidiasis harbor *C. albicans* in their vagina even at times when they are free of symptoms. Furthermore, heat shock proteins are present in their vaginal fluids indicating a persistent perturbation of the vaginal environment of women susceptible to recurrent vulvovaginal infections.

Given that a vaginal allergy renders a woman susceptible to vulvovaginal candidiasis, it seems clear that treatments aimed at alleviating the underlying immune predisposition may be beneficial to ending the cycle of recurrences. Unfortunately, at present there is no clearly defined treatment that is universally effective. Limited published studies as well as anecdotal evidence suggest several potential protocols that seem to be effective in a variable percentage of patients. If the offending allergen can be identified than avoidance of exposure usually results in elimination of recurrent symptoms. This may involve use of a condom in cases of seminal fluid allergy or changes in locally applied contraceptives or medications. In cases of allergic reactions to seminal fluid or to *C. albicans* successful systemic desensitization has been reported in limited studies. Other treatments have

involved blocking the allergic reaction at various stages: use of a mast cell stabilizer (cromolyn sodium) to inhibit histamine release, antihistamines to inhibit histamine binding to lymphoid cells, prostaglandin synthesis inhibitors to interfere with PGE_2 production.

An innate immune system component with strong anti-Candida activity is mannose-binding lectin (MBL). MBL is a plasma protein and a member of the collectin protein family MBL is defined as a pattern recognition molecule since it recognizes and binds to mannose-rich or N-acetyl-glucosamine-rich carbohydrate patterns on the surface of bacteria, fungi and viruses. Importantly, MBL does not bind to carbohydrate moieties present in human glycoproteins. Subsequent to MBL binding to a microbial surface, the complement system is activated and complement components are deposited on the surface of the affected microorganism. This makes the microbe susceptible to opsonization by complement receptor-bearing phagocytic cells. Binding and opsonization of MBL-bound microbes also accurs by binding to collectin receptors on macrophages. Additionally, complement activation can also lead directly to microbe killing by the creation of holes in the microbial cell wall. A decreased concentration of circulating MBL in some individuals is due to single nucleotide genetic polymorphisms in the MBL gene, located on chromosome 10. These variations interfere with effective aggregation of the MBL polypeptide chains resulting in a complex having reduced activity and stability. A recent analysis of MBL genotypes and vaginal MBL concentrations in women, demonstrated that possession of a mutant MBL genotype was associated with reduced MBL vaginal concentrations and an increased incidence of recurrent vulvovaginal candidiasis.

EFFECT OF SEXUAL INTERCOURSE ON VAGINAL IMMUNITY

Spermatozoa are viewed as foreign by the female immune system. Therefore, in order to preserve fertility, mechanisms have evolved to prevent women from developing antisperm immunity. Human seminal fluid has the highest concentration of PGE_2 of any body fluid and so semen is highly immunosuppressive. In addition, human seminal fluid is a potent inducer of IL-10, an inhibitor of cell-mediated immunity.

While preventing induction of immunity to spermatozoa, the immunosuppressive properties of seminal fluid may aid in the proliferation of pathogens in the vagina. If *C. albicans* is present in the vagina of a woman who then engages in sexual intercourse the deposition of semen will result in conditions favoring *Candida* proliferation and germination. Similarly, the female's immune response to microorganisms present in the male ejaculate may be inhibited by seminal fluid. Semen-induced immunosuppression may also explain the observation that, while antibiotic treatment of male partners does not reduce the incidence of bacterial vaginosis, sexual activity is an established risk factor for this condition.

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3
Anaerobic infections

Understanding of the events which combine to produce polymicrobial anaerobic infection is critical to effective antibiotic selection in obstetrics and gynecology. Polymicrobial infection usually requires polydrug antibiotic regimens.

CLASSIFICATION

Pasteur was the first investigator to demonstrate that microbial metabolism was possible without the absence of air. In 1857, he classified anaerobic bacteria into two groups. The first group he termed facultative anaerobes, which he defined as bacterial organisms that could grow either with or without air. The second group were designated as obligatory anaerobes. These were bacteria whose growth and viability were irreversibly impaired by air.

Approximately 146 technologic years later, we have not radically altered these basic concepts. The current classification scheme divides bacteria into three classes as shown in Table 3.1.

Each of these classification schemata is valid only in reference to the time of collection. For example, a strain of *Bacteroides fragilis* isolated from an ovarian abscess six weeks after vaginal hysterectomy will be a Class 3 extremely oxygen sensitive (EOS) organism; however, when recruited from the vaginal flora, it existed as a microaerophilic Class 2 bacteria. Under the environmental selection engendered by disease, the strain becomes a Class 3 (EOS) bacteria. Any breach of anaerobic technique at the time of collection or in the subsequent handling of the specimen would result in loss of the organism. However, once propagated *in vitro* under strict anaerobic conditions, the strain of *B. fragilis* will regain its original oxygen tolerance and can be handled outside the

Table 3.1 Classification of anaerobic bacteria

Class 1
Bacteria that grow better in the presence of air than in its absence.
Class 2
Bacteria that are unable to initiate growth unless the oxidation-reduction potential of the medium is low (the exception being when they are inoculated in large numbers).
Class 3
Bacteria that perish on even transient contact with atmospheric oxygen: **EOS** (Extremely Oxygen Sensitive) bacteria. These organisms are incapable of surface replication at oxygen concentrations of 0.5%.

anaerobic glove box without impairment of viability for up to four to six hours.

SOURCE OF THE BACTERIA

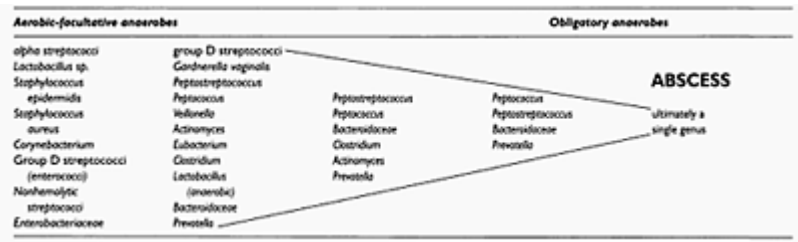
When anaerobic disease occurs, it is primarily due to bacteria derived from the patient's own microbiologic environment. Anaerobic bacteria constitute a significant component of the endogenous flora of our skin and most mucous membranes. In this context, man is his own reservoir of potentially pathogenic anaerobic bacteria.

PATHOGENESIS

The anaerobic progression

In the majority of instances in Obstetrics and Gynecology, anaerobic disease has its genesis with multiple bacteria whose abilities to replicate at different oxygen levels vary significantly. The catalytic event which takes an endogenous bacterial flora and gives it pathogenicity is an alteration in the oxidation-reduction potential of the microbiological environment. Normal healthy tissue has an oxidation-reduction potential of approximately +150 mV. Iatrogenic lowering of the oxidation-reduction potential often occurs during an operation when tissue is crushed by clamps, devitalized by loss of

Figure 3.1 The anaerobic progression



blood supply, and/or subjected to microhematoma formation or the development of serous fluid collection.

A given disease can similarly lower the oxidation-reduction potential and thus initiate the anaerobic progression. With the lowering of the oxidation-reduction potential, acidification of the local environment and removal of molecular oxygen, the polymicrobial flora of disease undergoes selective changes. The more aerobic bacteria (which cannot replicate under these progressively adverse conditions) undergo a process of sequential autoelimination. This process is termed the anaerobic progression (Figure 3.1). Abscess formation is the ultimate culmination of the anaerobic progression. From well developed abscess material usually only a single genus of bacteria is isolated.

The immediate anaerobic syndrome

The anaerobic progression is the major but not sole pathway to anaerobic disease. The appropriate oxidation-reduction potential can be combined with the right bacterium or bacteria to produce anaerobic infection, i.e., ahematoma contaminated with a major Class 2 anaerobe or iatrogenic or spontaneous penetration of the gastrointestinal tract. In these instances, there is no need for alteration of the microbiological environment to initiate the disease process since it already is present (e.g. feces has the lowest oxidation-reduction potential recognized, minus 200 mV, and the gastrointestinal anaerobic flora has a hundred-fold dominance over its Class I counterpart).

DIAGNOSIS

The diagnosis of polymicrobial (aerobic-anaerobic) disease is usually inferred from the clinical situation. The clinical setting in which disease occurs dictates the presumptive diagnosis (Tables 3.2, 3.3). For example, postpartum endometritis following cesarean section may be due to a monoetiological agent like the group A beta-hemolytic streptococci; however, in the majority of instances, disease has its genesis with the anaerobic process. Some of the clinical clues which should suggest advanced anaerobic infection include:

(1) presence of foul-smelling discharge;
(2) failure to achieve the anticipated therapeutic response with the combination of a penicillin and an aminoglycoside in the absence of a surgically amenable focus of infection;
(3) failure of bacteria visualized on Gram stain to grow from purulent material;
(4) the development of septic thrombophlebitis.

Clinically, the most useful clue is foul-smelling discharge. The odor is caused by the cleavage of -SH groups from amino acids which occurs only under strict anaerobic conditions. More advanced disease (abscess

Table 3.2 Clinical situations commonly associated with polymicrobial infections

Obstetrics	**Gynecology**
Septic abortion	Pelvic cellulites
Infected ectopic pregnancy	Cuff abscess or cellulites
Retained products of conception	Ruptured tubo-ovarian abscess
Post-cesarean section endomyometritis	Postoperative abdominal wound infections
Postpartum endometritis associated with obstetrical trauma	

Table 3.3 Appropriate specimen for anaerobic cultures in obstetrics and gynecology

Specimen	***Technique***
Abscess (cuff, ovarian, tubo-ovarian, Bartholin's gland, etc.)	Aspiration
Peritonitis (pelvic inflammatory disease, uterine perforation, etc.)	Aspiration via culdocentesis
Buboes (lymphogranuloma venereum, etc.)	Direct aspiration
Septic abortion, ruptured tubo-ovarian abscess	Tissue
Deep wounds direct aspiration	Tissue

formation) of the immediate anaerobic syndrome is usually clinically evident.

Specimen selection

It is very important to avoid contamination of the diagnostic specimen by bacteria inherently present on skin and mucous membranes. Since the anaerobes causing anaerobic disease are derived from the endogenous bacterial flora, it is pointless to collect specimens from a site which requires the sampling vehicle to have contact with an area that has an endogenous bacterial flora.

Specimen collection

Good anaerobic bacteriology is time consuming and expensive. Therefore, it is important that only specimens which have been appropriately selected and properly collected be submitted for anaerobic culture. A bad specimen will not only give useless or misleading results, it will also prevent the laboratory personnel from devoting sufficient attention to valid specimens.

An appropriate culture for anaerobic progression is normally obtained by aspiration with a needle and syringe. Great care must be taken to exclude air. Even transient contact with molecular oxygen is as lethal as an autoclave for Class 3 anaerobes. In selected instances, e.g. ruptured tubo-ovarian abscess or gangrenous wound infections, it is not possible to obtain a specimen for bacteriological analysis by aspiration. In these circumstances, a fragment of infected tissue constitutes a valid specimen. Any time a cotton swab (even one stored in a tube free of molecular oxygen) is exposed to room air in the course of obtaining a culture sample, concern must be given to the validity of the specimen. Of even greater concern is the necessity to sample an area with an inherent bacterial flora. The only reason to obtain bacteriological cultures in these circumstances is not to identify the constituents of the **Anaerobic Progression** but rather to exclude the presence of exogenous aerobic bacteria which may have epidemiological or nosocomial significance, i.e., *Neisseria gonorrhoeae*, *group* A streptococci, *Listeria monocytogenes*.

Role of the Gram stain

Next to the physician's ability to anticipate when the anaerobic progression is functioning, the most important diagnostic tool is the Gram stain. When dealing with a well established abscess, the ocular-cerebral reflex is almost as accurate as an anaerobic diagnostic facility. Whenever you take an anaerobic culture, make a Gram stain (Table 3.4).

Table 3.4 Differential diagnosis of anaerobic bacteria from the abscess pus based on Gram stain morphology

Coccus		***Bacillus***	
Gram-positive	***Gram-negative***	***Gram-positive***	***Gram-negative***
Peptostreptococci (anaerobic streptococci) pairs and chains	***Veillonella*** pairs or clusters	***Clostridia*** large straight rods (boxcars)	***Bacteroides/Prevotella*** small staining round ends
Peptococci (anaerobic staphylococci) clusters		***Actinomyces*** filamentous growth	***Fusobacterium*** pointed ends or filaments
			Eubacteria slender rods
			Propionibacteria (anaerobic *Corynebacteria*) banding, beading, clubbing; V-Y arrangement; Chinese letters

THERAPY—GAINESVILLE CLASSIFICATION

When confronted clinically with the anaerobic progression, in the majority of instances antibiotic selection cannot be guided by bacteriological cultures. The problems with specimen collection, specimen handling and a dynamic pathogenic flora (the anaerobic progression) are not readily addressed in diagnostic bacteriology laboratories. These problems have led to the creation of the **Gainesville Classification**. The **Gainesville Classification** subdivides the polymicrobial flora which function in the anaerobic progression into its first four categories.

The concept of **Category Designation** must be concurrently used. Category designation equates with the ability to eradicate >94% of the bacteria within that category.

The bulk of clinical isolates belongs to Category I-A and I-B of the **Gainesville Classification** (Table 3.5). Since the majority of the bacterial isolates are susceptible to penicillin and/or its semisynthetic analogue, the prior success of obstetricians and gynecologists with such simple therapy as ampicillin alone or penicillin and an aminoglycoside is readily comprehensive.

Table 3.5 Gainesville Classification

Anaerobic bacteria
Category IB
Anaerobes for which penicillin is the drug of choice for highly effective therapy.
Category II
The nonpenlcillin-sensitive anaerobic bacteria which includes most strains of *Bacteroides fragilis* and *Prevotella species (bivia, disens).*
Aerobic bacteria
Category IA
The Gram-positive aerobic bacteria.
Category III
The group D streptococci—specifically the enterococci.
Category IV
The Gram-negative aerobic rods of the *Enterobacteriaceae*.

The effectiveness of antimicrobial therapy for polymicrobial anaerobic disease is influenced by the prevailing oxidation-reduction potential. If the oxidation-reduction potential is not in a critical zone which will sustain the successful replication of pathogenic Class 2 anaerobic bacteria, the ongoing polymicrobial disease can be effectively aborted by the eradication of the majority of the dominant constituents which are predominantly Class 1 anaerobes. However, once a critical oxidation-reduction potential is achieved, partial eradication of the bacteria present will not abort progression of disease. At this point, it becomes necessary to eradicate all existing anaerobic bacteria in Category IB and Category II.

SURGICAL INTERVENTION

How aggressive the clinician must be surgically is dictated in part by his understanding of the anaerobic progression and the immediate anaerobic syndrome. In dealing with potentially life-threatening disease, there will be isolated instances where, given a choice between all-encompassing antibiotic coverage and the Bard-Parker blade, one must

preempt surgical intervention over medical therapy. Retained products of conception in association with thrombophlebitis, an ovarian abscess or a ruptured tubo-ovarian abscess are examples of situations in which the adverse microbiological environment must be mechanically removed or disrupted to achieve a therapeutic cure. It cannot be stressed too strongly that where there is necrotic tissue or a significant abscess, rarely can a bacteriological cure be achieved with antibiotic therapy alone. However, once a surgically amenable focus of infection has been excluded, a commitment can be made to attaining a non-operative medical cure.

ANTIBIOTIC SELECTION FOR POLYMICROBIAL ANAEROBIC DISEASE

When dealing with polymicrobial disease, the major therapeutic commitment must be to Categories I, II and IV if the principal morbid sequelae (septicemia, septic thrombophlebitis and abscess formation) are to be averted. Confronted with life-threatening polymicrobial disease, the antibiotic selection is that of triple therapy (classically penicillin or ampicillin, clindamycin or metronidazole and an aminoglycoside) or its equivalent. Triple therapy gives you ++++1/2 to +++++ in each category of the **Gainesville Classification,** thus creating "an antibiotic stone wall". When medical failures occur, they are due to a beta-lactamase, a clindamycin-resistant or aminoglycoside-resistant strain of *Staphylococcus aureus*, a clindamycin-resistant strain of *Bacteroides fragilis* or a multiresistant-*Enterobacteriaceae*. Being aerobic bacteria, *Staphylococcus aureus* and the *Enterobacteriaceae* will be identified by conventional bacteriological cultures. The concept of triple therapy was designed to give obstetricians and gynecologists the ultimate ability to dissect out medically amenable disease from that requiring surgical intervention.

Early in the course of postoperative infectious complications, the clinician usually is not dealing with life-threatening disease, but rather with the anaerobic progression. The effectiveness of antimicrobial therapy for polymicrobial disease is influenced by the existing oxidation-reduction potential. When that potential is not in a critical zone, anaerobic infection can be effectively dealt with by the eradication of the major constituent of the facilitating bacterial flora in the anaerobic progression. Once a critical oxidation-reduction potential is reached, partial eradication of the bacterial flora present will not abort disease. It becomes necessary to eradicate all bacterial constituents.

The majority of postoperative infectious complications should be treated aggressively with two-drug therapy which effectively and completely (+++1/2 to ++++) covers two or more categories in the **Gainesville Classification**. Initial selection of the antimicrobial agents is often dictated by the disease entity *per se*. No matter what combination of drugs is used, the clinician must be cognizant of the GAPS, in terms of the **Gainesville Classification,** of his or her antibiotic selection. If the anticipated therapeutic response does not develop in 24–36 hours, the antibiotics necessary to effectively cover the categorical gaps should be substituted.

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4
Antibiotic selection in Obstetrics and Gynecology

Why do the ground rules covering antibiotic selection in Obstetrics and Gynecology differ from those of Internal Medicine?

The internist deals with infectious diseases that are primarily monoetiological: a single organism is responsible for a given set of symptoms. While the obstetrician/ gynecologist also deals with monoetiological disease, its pathogenic spectrum is often different. The principal pattern in Obstetrics and Gynecology is polymicrobial infection which primarily involves microaerophilic and obligatory anaerobic bacteria. When the 10 most common bacterial pathogens for the internist and the obstetrician/gynecologist are compared, the degree of overlap is not significant. On the other hand, when bacterial isolates from the intravascular compartment are contrasted, the differences are obvious (Table 4.1).

Even when the two disciplines are dealing with the same genus of bacteria, the spectrum of disease may diverge significantly (e.g. the group A beta-hemolytic streptococci). In regard to the obstetrician/gynecologist, this means post-IUD-insertion endometritis, postpartum endometritis/peritonitis (puerperal sepsis), or Meleny type I ulcer (necrotizing fasciitis). These are not the typical clinical presentations of the group A beta-hemolytic streptococci for the internist. Nevertheless, the basic ground rules for both disciplines are the same (Table 4.2).

The dominant cleavage factor between Internal Medicine and Obstetrics and Gynecology is the prevalence of polymicrobial infection and the potential for participation by the penicillin-resistant *Bacteroidaceae*.

ANTIBIOTIC SELECTION FOR MONOETIOLOGICAL DISEASE

The rule governing antibiotic selection states that for monoetiological disease, use the drug of choice. When infection is due to group A or B beta-hemolytic streptococci, *Listeria monocytogenes, Neisseria gonorrhoeae, Mycoplasma hominis,* etc., it is primarily monoetiological disease. Sometimes, monoetiological disease may be due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae,* or the Gram-positive cocci. The initial antibiotic selection must anticipate the probable spectrum of offending organisms, as well as the drug of choice concept.

In those instances of monoetiological disease with a broad spectrum of potential pathogens (e.g. urinary tract infection, chorioamnionitis, primary pneumonia),

Table 4.1 Septicemic bacterial isolates (Shands Teaching Hospital)

Frequency of isolates	***Medicine***	***Obstetrics***
1	*Staphylococcus aureus* (21%)	*Bacteroidaceae* (17%)
2	*Escherichia coli* (18%)	*Gardnerella vaginalis* (17.5%)
3	*Pseudomonas* (16%)	Anaerobic (10.8%) streptococci
4	*Klebsiella pneumoniae* (8.7%)	Streptococci (10.8%) groups A&B
5	*Proteus* (7.6%) (indole-positive & negative)	Enterococci (10.8%)
6	Enterococci (6.4%)	*Escherichia coli* (6.7%)

Table 4.2 Basic ground rules in antibiotic selection

(1) The antibiotic or antibiotics selected must be highly effective, if not drug of choice against the presumed etiological agent or agent. (Drug of choice vs. best fit for potential pathogen spectrum)

(2) Antibiotic selection must be done with patient safety as being a foremost consideration

(3) Antibiotic selection must be able to achieve therapeutic concentrations at the site of infection

(4) Proper determination of dosage must be calculated to avoid dose-related adverse drug reactions. Adjustments include:

- body weight
- route of administration
- functional status of the principal mode of detoxification
- patient's physiological status i.e. pregnancy, third-space pooling

(5) Consideration should be given to the frequency of administration

(6) An anticipated therapeutic response needs to be projected

the rule governing antibiotic selection is: the best drug for the anticipated spectrum. This may necessitate two-drug therapy when disease is potentially life-threatening (e.g. maternal chorioamnionitis with septicemia). In certain instances, monoetiological diseases may be transformed into polymicrobial infection. For example, with acute endometritis/salpingitis/peritonitis due to *N. gonorrhoeae*, when peritonitis is well established, anaerobic superinfection from organisms derived from the vaginal flora may occur. A broader spectrum of coverage would be indicated.

Chorioamnionitis, in its initial phase, is due to a single organism, usually a facultative anaerobe, such as a motile member of the *Enterobacteriaceae* or the virulent cocci (i.e., the group A beta-hemolytic streptococci or *N. gonorrhoeae*). The divergent antibiotic

susceptibility patterns and the potential ramifications of disease, if allowed to evolve, argue for the combination of two drugs. Therapy for a gravida involves two biologically unique individuals.

In chorioamnionitis, it is necessary to treat the potential fetal/neonatal as well as the maternal infection. Because of its augmented ability to attain significant levels in amniotic fluid and cord blood, ampicillin is substituted for penicillin. The therapy of choice is the

Table 4.3 Gainesville Classification

Anaerobic Progression Portion **Category I—A & B**
Penicillin-sensitive aerobes (A) and anaerobes (B)
Category II
Penicillin-resistant anaerobes
Category III
Community-acquired enterococci
Category IV
Community-acquired *Enterobacteriaceae*
Nosocomial Disease Portion **Category V**
Multi-resistant *Enterobacteriaceae*
Category VI
Pseudomonas species
Category VII
Methicillin-resistant staphylococci

combination of ampicillin and an aminoglycoside, preferably gentamicin. In this instance, fetal considerations modify maternal therapy

ANTIBIOTIC SELECTION FOR NOSOCOMIAL, MONOETIOLOGICAL DISEASE

Septicemia in intensive care units is usually monomicrobial in etiology; however, the ability to document causation in a clinically meaningful time frame is lacking. Most causes of nosocomial septicemia are aerobic bacteria belonging to categories V, VI and VII of the Gainesville Classification (Table 4.3).

Like the obstetrician/gynecologist confronted with life-threatening disease, the physician in the intensive care unit resorts to ‘triple therapy’:

• imipenem for Categories I, IV, and V

• amikacin for Categories IV, V, and VI
• vancomycin for Categories I and VII

The governing concept of antibiotic selection in Obstetrics and Gynecology for life-threatening disease is the need to cover with category encompassing antibiotics, Categories I through IV The governing concept for Internal Medicine is best category-fit-for-spectrum encompassing potential pathogens.

Table 4.4 Clinical situations commonly associated with polymicrobial infections

Obstetrics	**Gynecology**
Septic abortion	Pelvic cellulitis
Infected ectopic pregnancies	Cuff abscess or cellulltis
Retained products of conception	Ruptured tubo-ovarian abscess
Postcesarean-section endometritis	Cul-de-sac abscess
Postpartum endometritis	Postoperative abdominal wound infections

ANTIBIOTIC SELECTION FOR POLYMICROBIAL COMMUNITY-ACQUIRED DISEASE

The effectiveness of antimicrobial therapy for polymicrobial infection is influenced by the existing oxidation-reduction potential. When the oxidation-reduction potential is not yet in a critical zone, anaerobic infection can effectively be dealt with by eradicating the major constituent of the facilitating bacterial flora in the anaerobic progression. In this situation, it is not necessary to eradicate each bacterial constituent. Once a critical oxidation-reduction potential is achieved, partial eradication of the bacteria present will not abort disease.

The presumptive clinical diagnosis alerts the physician that he or she is dealing with a polymicrobial infection (Table 4.4). In dealing with anaerobic polymicrobial infection, antibiotic coverage should be directed at the first four major categories of the Gainesville Classification schemata (Table 4.3).

While focusing on the anaerobic participants in the anaerobic progression, the first four categories of the Gainesville Classification effectively deal with the predominantly aerobic bacteria which may be involved in obstetrical or gynecological infections. The multidrug-resistant *Klebsiella* and *Pseudomonas* are rarely a problem for the obstetrical or gynecological patient unless the patient has been in the intensive care unit for long periods of time or has been subjected to complex medical care which biases her for the potential acquisition of nosocomial infection. The aerobic bacteria involved in obstetrical and gynecological infections can usually be effectively dealt with by penicillin or a semisynthetic analogue and an aminoglycoside.

When polymicrobial infection associated with a surgically amenable focus of infection cannot be identified, then the first four categories of coverage (Gainesville Classification) needs to be instituted in the case of life-threatening anaerobic infection. If abscess

formation has occurred, surgical intervention is required. It cannot be stressed too strongly that where there is necrotic tissue or abscess, a bacteriologic cure with antibiosis alone can rarely be achieved.

Assuming exclusion of microbiological situations amenable to surgical therapy in which a critical oxidation-reduction potential is present (i.e., ruptured tubo-ovarian abscess, retained products of conception, etc), triple therapy (penicillin- or ampicillin-clindamycin-aminoglycoside) or an equivalent is indicated for lifethreatening disease.

Three (+++) to four (++++) types of coverage must be achieved in each of the therapeutic categories. When dealing with the anaerobic progression, any combination of drugs which gives you at least a +++ coverage for the penicillin-sensitive anaerobes and ++ to +++ coverage in the remaining three categories is recommended (Tables 4.5, 4.6, 4.7).

If the first four categories are covered effectively, an antibiotic stone wall is created for aerobic/anaerobic polymicrobial infection. This permits the evaluation of current and future antibiotics in terms of delineating the existing gaps. Whenever a given antibiotic is used, the physician must be cognizant of the gaps. If the anticipated therapeutic response does not occur and there is not a surgically amenable or manageable focus of infection, it is imperative to close the gap with appropriate therapy. The system is designed to give obstetricians and gynecologists the ability to dissect out medically amenable disease from that requiring surgical intervention.

ANTIMICROBIAL RESISTANCE

In the future, antibiotic selection will be influenced by the emergence of antimicrobial resistance. This phenomenon and its spread represent the convergence of a

Table 4.5 Spectrum of coverage achieved within the Gainesville Classification by antibiotics with Category I designation

	Gainesville Classification categories			
Category I Antibiotics	***I***	***II***	***III***	***IV***
Penicillins				
First generation	++++	−	+++	+−++
Second generation	++++	−	++++	++
Third generation	++++	++-+++	++1/2	++1/4
Fourth generation	++++	++-+++	+++	++1/2
Fifth generation	++++	+++	++++	+++
Cephalosporins				
First generation	+++	+/−	+	++1/4

Second generation	++++	++–+++	+	++1/2
Third generation	+++	++	+–++	+++1/4
Erythromycins	++++	–	+++	+
Vancomycin	++++	–	+++	–
Imipenem/Cilastatin	++++	+++	+++	++++

Table 4.6 Coverage within the Gainesville Classification of antibiotics with Category II designation

	Gainesville Classification categories				
Category II Antibiotics	***IA***	***IB***	***II***	***III***	***IV***
Clindamycin	+++	+++1/2	++++	–	–
Metronidazole	–	+++	++++	–	–
Imipenem/Cilastatin	++++	+++1/2	+++	+++	++++
Ampicillin/Sulbactam	++++	+++1/2	+++	++++	++ – +++
Ticarcillin/Clavulanate	+++	+++1/2	+++	++	++–+++
Piperacillin/Tazobactam	++++	+++1/2	+++	+++	+++

Table 4.7 Coverage within the Gainesville Classification of antibiotics with Category III efficacy

	Gainesville Classification categories				
Category III Antibiotics	***IA***	***IB***	***II***	***III***	***IV***
Penicillins	++++	++++	–	+++	+
Erythromycins	++++	+++	–	+++	+
Chloramphenicol	++	+++	++++	+++	++
Trimethoprim/ Sulfamethoxazole	+++	+++	+	+++	++

variety of factors which include mutations in common resistance genes, the exchange of genetic information among microorganisms, and the selective pressures engendered by antibiotic utilization both in hospitals and within the community. By becoming stably endemic a number of multiresistant bacterial phenotypes have impacted or have the potential to impact on obstetricians and gynecologists (Table 4.8).

Multiresistant *N. gonorrhoeae* and *Streptococcus pneumoniae* have become well established in the community. Multiresistence for these bacteria to beta-lactam and non-beta-lactam antibiotics is not the result of common

Table 4.8 Multiresistant bacteria potentially impacting on Obstetrics and Gynecology

Enterococcus faecalis
Neisseria gonorrhoeae
Stahylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

resistance mechanisms or genetic linkage. What happen is the clonal spread of relatively few beta-lactam resistant strains. A small percentage of these bacteria also expressed resistance to one or more non-betalactam antibiotics. When the beta-lactam strains became endemic, switching antibiotic therapy selected for increased antibiotic resistance to non-beta-lactam antibiotics.

The mechanism of beta-lactam resistance of *N. gonorrhoeae* involves both chromosomal and plasmidmediated mechanisms. The mechanism of beta lactam resistance of *S. pneumoniae* is plasmid-mediated alterations in high molecular weight cell wall penicillinbinding proteins.

Hospital multiresistant bacteria

Among Gram-positive bacteria, the most common mechanisms for exchange of genetic material involve transformation and transduction, whereas with Gram-negative bacteria conjugation is the most commonly recognized mode of genetic transfer.

Multiresistance, and in particular that to vancomycin, of *Enterococcus faecalis* is borne on mobile plasmids and transposons. Not all resistance genes that transfer among bacteria are expressed or maintained. The frequent use of vancomycin in the 1990s for therapy of methicillin-resistant *Staphylococcus aureus, Clostridium difficile*, and in-line bacteremia caused by coagulase-negative staphylococci was the predominant selective pressure that resulted in the development and spread within hospitals of vancomycin-resistant enterococci. The intensity of use of vancomycin is proportional to resistance levels in bacteria within hospital settings. The selective pressure caused by vancomycin utilization has impacted on *S. aureus and S. epidermidis*.

Physicians need to monitor local antibiotic resistance patterns. Confronted with life-threatening disease within the disease spectrum of a multiresistant bacteria or a 10% resistance to a given a potential multiresistant bacteria within a hospital or community, antibiotic selection should conform to “best-fit-for-spectrum” of all significant pathogens.

5
Antibiotics and pregnancy

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MATERNAL-FETAL DISTRIBUTION

The transport of drugs is governed by diffusion, surface area available for transfer, lipid solubility, molecular weight, degree of ionization, partition coefficient, and maternal-fetal concentration gradient. The availability of a drug for transport is dependent, in turn, on the binding of the drug to the plasma proteins. Forming a drug-protein complex is contingent upon covalent and ionic bonding between polar and nonpolar groups on the antibiotic and upon the polarity of amino acids available for binding. The unbound fraction in the serum is pharmacologically active and in a state of dynamic equilibrium with the drug present in the extra-cellular space. As free drug is excreted or metabolized, protein-bound drug is released so as to maintain a relatively constant proportion of free drug. Serum protein levels do not influence the eventual utilization of all of the drug present in the plasma, but rather determine the amount of free drug available at any given moment. Only the unbound drug passes freely across membranes separating biologic compartments. It is this form of the drug which is capable of antimicrobial action. The affinity of plasma proteins for a specific drug is not necessarily indicative of its binding capacity. Certain carrier proteins may have a high affinity for a given drug but a relatively low binding capacity. When the binding sites are saturated, a secondary plasma protein usually participates in the reaction, even though its binding affinity is lower. Different drugs may compete for the same binding site on a protein molecule. The unbound plasma levels will be increased if the bound form on a protein molecule is displaced by another drug with a greater affinity for that particular binding site. Once the free form of the drug has entered into a given biologic compartment, such as the fetal intravascular space or the amniotic fluid, it is again subjected to the binding ratios of those proteins present. The lack of a significant amount of protein in certain biologic compartments such as the cerebrospinal fluid (CSF) and amniotic fluid may account for the relative efficiency of certain drugs in eradicating bacteria, despite the low concentrations achieved relative to those in the corresponding vascular compartment. The significance of protein binding is brought into sharp focus when therapy is initiated for the fetus rather than the mother. Because of its protein binding, the distribution of ampicillin is such that it is often the drug of choice in terms of first-line fetal therapeutics.

Recent evidence has demonstrated that placental drug transport may also be regulated by transporters expressed in the placenta, particularly efflux transporters that serve to ‘pump’ drug back to the mother, limiting fetal exposure. Several efflux transporters have been identified in the human placenta with P-glycoprotein (MDR1) being the most studied. Many drugs are transported by the P-glycoprotein transporter, including drugs such as digoxin that are used for *in utero* treatment. However, transporters from the multidrug resistance-associated protein (MRP) family as well as the breast cancer resistance protein (BCRP/MXR/ABCP) have also been found in human placenta. The MRP transporters appear to prefer organic anions drugs, glutathione conjugates,

glucuronate conjugates, uronates and sulfates. Though less understood, the BCRP transporter appears to transport compounds such as topotecan and mitoxantrone and probably other drugs. Because these transporters pump drug back to the mother from placenta tissue, they can serve a protective role following maternal drug exposure. However, in

Table 5.1 Congenital infections for which antimicrobial therapy exists

	Organism	***Drug of choice***
Bacteria	*Listeria monocytogenes*	Ampicillin
	Haemophilus influenzae	Ampicillin
	Salmonella typhi	Ampicillin
Spirochetes	*Treponema pallidum*	Penicillin
Protozoan	*Toxoplasma gondii*	Pyrimethamine and sulfonamides

some cases, *in utero* drug treatment is desired (e.g., intra-amniotic infection, HIV or cardiac conditions) and these transporters may limit fetal exposure and thus reduce drug efficacy.

The placenta also possesses limited capabilities to metabolize compounds via both oxidative metabolism pathways (e.g. cytochrome P450 enzymes) or via drug conjugation pathways (e.g. glucuronosyl transferases or glutathione S-transferases). In most cases, metabolism by these pathways results in the production of inactive and more easily excreted metabolites. However, in some cases, reactive or toxic metabolites may be produced (see below). Substantial research in this area has focused on the inducibility of placental oxidative enzymes (e.g. cytochrome P450 1A1) in mothers who smoke during pregnancy. In pregnant women who smoke, placental cytochrome P450 1A1 has been shown to be induced up to 100-fold as compared to the basal state. This is especially important since cigarette smoke contains a number of polycyclic aromatic hydrocarbons that are metabolized to produce reactive metabolites that can be mutagenic or carcinogenic. However, the glutathione S-transferase enzymes, which are not induced by cigarette smoking, can conjugate glutathione with these polycyclic aromatic hydrocarbon reactive metabolites. Thus, an imbalance can result in women who smoke, potentially placing the fetus at additional risk.

Though not studied extensively, oxidative enzymes such as cytochrome P450 1 Al and conjugative enzymes such as glutathione S-transferase and glucuronosyl transferases may also participate in the metabolism of drugs given for *in utero* treatment of various fetal disorders. Though at the present time limited research is available regarding the activities of these enzymes in placental tissue toward commonly used drugs, it is reasonable to assume that they would affect maternal-fetal distribution.

ANTIBIOTICS FOR THE FETUS

The obstetrician is in the unique position of being simultaneously a therapeutician for both the mother and fetus. The mother and fetus are biologically unique individuals whose ability to metabolize a drug or be adversely affected by the compound or its degradative derivatives may differ significantly.

Certain antibiotics which would constitute drug of choice for the non-pregnant female must be **avoided** during gestation due to their ability to act as potential **teratogens,** induce drug **embryopathy** in the fetus or cause an adverse reaction in the enzymatically immature neonate.

Antibiotic therapy for congenital infection *in utero*

Selected organisms which have the ability to traverse the placenta and establish congenital infection in the fetus are responsive to maternal antimicrobial therapy (Table 5.1).

Chorioamnionitis complicates 1–5% of term pregnancies. The incidence of intra-amniotic infection approaches 25–40% of cases of preterm labor and is a major contributor to increased maternal and fetal morbidity and mortality. Although chorioamnionitis may result from hematogenous dissemination of systemic disease, most cases are caused by ascending infection from the vagina and are frequently polymicrobial. *Listeria monocytogenes* is a classic example of descending or hematogenous infection whereas *Escherichia coli, Bacteroides* species, anaerobic streptococci and group B streptococcus are commonly associated with ascending intra-amniotic infection. Prolonged labor, membrane rupture of greater than 12 hours and multiple vaginal examinations may be contributing factors.

Little data exist to guide the clinician as to when to initiate antibiotic therapy or the optimal time frame for delivery. A literature review reveals only two randomized clinical trials comparing antibiotic regimens and neither was placebo controlled. Gibbs *et al.,* in a randomized trial, enrolled 48 women to receive either ampicillin or gentamicin. Mayberry *et al.* also used ampicillin and gentamicin but added clindamycin to one arm of the study. The results reported were that intrapartum use of antibiotics was associated with a reduction in neonatal sepsis and pneumonia, but the results did not reach statistical significance. No difference in the incidence of maternal bacteremia was noted. A trend towards a lower incidence of postpartum endomyometritis was noted in those receiving triple antibiotic therapy but the results did not reach statistical significance. Meta-analysis by Hopkins and Small of these two studies is inconclusive regarding the choice of antibiotic regimens to treat intra-amniotic infection.

The use of antibiotics as an adjunct to tocolysis in the management of preterm labor with intact membranes remains controversial. Data from 13 randomized trials meeting the criteria for a meta-analysis produced variable results with limited improvement in both prolonging gestation and increasing the birth weight. The efficacy of antibiotic use in cases of preterm labor with intact membranes is lacking and fails to show a true benefit from their use.

Untreated asymptomatic bacteriuria appears to play a role in preterm labor and delivery. A meta-analysis of the treatment results of asymptomatic bacteriuria revealed a direct relationship of this entity and preterm birth. A significant benefit of treating asymptomatic bacteriuria in addition to prevention of pyelonephritis has been shown.

An association has been demonstrated between bacterial vaginosis and preterm labor in high risk populations. However, this association has not been confirmed in low risk populations with asymptomatic bacterial vaginosis.

The literature does not support routine use of antibiotics as an adjunct to tocolytic agents in the management of a woman with idiopathic preterm labor. There is a consensus, however, that sexually transmitted diseases, group B streptococcus colonization, asymptomatic bacteriuria and symptomatic bacterial vaginosis should be treated with the appropriate antimicrobial therapy. Eradication of group B streptococcal colonization of the genitourinary tract in pregnancy has been shown to be unsuccessful and treatment is usually delayed until labor. The other infections are best treated at the time they are diagnosed.

ADVERSE DRUG REACTIONS IN PREGNANCY

Antimicrobial therapy in pregnancy assumes the concept that drug action will occur within not one, but two, biologically unique individuals. As a general rule all drugs are more toxic in the fetus than in infants or adults. Antibiotics may have such deleterious effects on the fetus that their very use in pregnancy is openly questioned (Table 5.2).

TETRACYCLINES

The tetracyclines have two major effects:

(1) they inhibit protein synthesis by interfering with the transfer of amino acids from aminoacyl RNA to polypeptides; and
(2) they act as efficient chelators of heavy metals, in particular, calcium.

Adverse fetal or maternal effects of tetracycline are mediated by one or both of these mechanisms.

Although the deleterious consequences of the tetracyclines are related to total dosage and duration of administration, the types of adverse drug reactions occurring in pregnancy are such that there is to all intents and purposes no time which is deemed safe for their therapeutic administration. Although there are

Table 5.2 Antibiotics contraindicated in pregnancy

Tetracyclines
In the first trimester, if administered during osseous organogenesis, may induce thalidomide-like deformities. In the second and third trimesters, will induce an embryopathy affecting bone growth and primary and permanent dentition.

The old generation tetracyclines, if administered to a gravida with occult renal compromise or acute pyelonephritis, may induce fulminating hepato-renal decompensation.
The tetracyclines are effective chelators of heavy metals. They are competitive at the osteoblastic level with calcium in the areas of new bone formation. Their presence impedes the incorporation of C14-proline into a cartilage as well as of Ca46 into the organic matrix of bone. This action results in the inhibition of bone growth (Figures 5.1 & 5.2).

Chloramphenicol

Due to enzymatic immaturity resulting in a relative inability to conjugate compound for bioelimination, free unconjugated drug acts to produce a clinical pattern of cardiopulmonary collapse termed 'the gray-baby syndrome'.
As long as the fetus resides *in utero* there is no adverse effect resulting from maternal administration of the drug.

Quinolones and fluoroquinolones

The quinolones and fluoroquinolones produce permanent cartilagenous defects in the bones of animal fetuses and growing juveniles.

Sulfonamides

If administered immediately prior to parturition, can achieve cord levels comparable to those observed in maternal serum. The sulfonamides can displace bilirubin from its albumin carrier. The bilirubin thus freed has the ability to traverse the neonatal blood-brain barrier and occasionally induce kernicterus.

Trimethroprim

These antimicrobial compounds have been shown to be teratogenic in animal model systems. While there is no data to document teratogenicity for the human fetus, it is best to avoid their use in pregnancy.

Metronidazole

The drug is an excellent mutagen. Data derived from animal model systems has demonstrated oncogenic potential for selected strains. Drug use in pregnancy or during breastfeeding must be carefully evaluated in terms of maternal benefits versus theoretical fetal/neonatal risks.

Streptomycin

Adversely affects subsequent neonatal cochlear function. The effect is dose related.

individual toxicologic variations between the several tetracyclines, for discussion purposes they are considered a group.

Fetal considerations

Throughout the three trimesters of gestation, the tetracyclines are contraindicated because of fetal considerations (Table 5.3). The evidence derived from animal model systems is almost as incriminating as that which existed for thalidomide prior to the massive experiment in human teratology, Administration of a tetracycline during the period of osseous organogenesis in an animal may result in hypoplasia of the anterior limb buds with micromelia and other skeletal abnormalities. It would be presumptuous to interpret

experiments in animals as being directly analogous to man. Nevertheless, clinical reports suggest that a relationship exists and that these observations can be extrapolated from rats, rabbits, and chickens and applied to man. Carter and Wilson reported on a group of 13 mothers who were given large doses of tetracycline in the first 12 weeks of pregnancy, of whom six had malformed babies. Similarly, Woollam and Miller reported the occurrence of four malformations in the offspring of 37 women who received comparable doses of tetracycline.

While bone is the major fetal site of tetracycline action, it is not the sole target organ. In teeth, tetracycline enters the developing tooth substance roughly in proportion to the amount of crystalline surface rather

Table 5.3 Unique adverse drug reactions observed with tetracycline administration in pregnancy

First trimester
Fetal considerations: probable teratogen, with induction of micromelia and other skeletal abnormalities.
Second trimester
Fetal considerations: tetracycline embryopathy; inhibition of bone growth; abnormal formation of deciduous teeth.
Third trimester
Fetal considerations: continued tetracycline embryopathy; deposition within deciduous teeth and bones*. Maternal consequences: hepatic fatty metamorphosis*.

*Associated with IV administration in patients with pyelonephritis or renal impairment.

than in proportion to the calcium content. Dental injury occurs if tetracycline is administered when the crowns of the deciduous anterior teeth are being formed, which is from midpregnancy to about the sixth month of postnatal life. This phenomenon translates as hypoplasia of deciduous teeth and intrinsic staining of the enamel. The degree of discoloration and hypoplasia are both dose-dependent.

Maternal considerations

There is a well-defined syndrome of fulminating hepatic decompensation described in women treated for pyelonephritis with large intravenous doses of tetracycline. Characteristically the syndrome occurs during the last trimester of pregnancy. The women have jaundice, severe nausea and vomiting, hematoemesis, abdominal pain, and headaches, and they may lapse into coma. Death is not an unusual outcome. The clinical course of the entity is often indistinguishable from acute fulminating viral hepatitis in pregnancy. Distinction between the two diseases is often on the basis of liver biopsy. Microscopic examination of the liver reveals widespread small intracytoplasmic triglyceride-rich vacuoles within hepatocytes (Figure 5.3). Sheehan, in his original

description of this disease entity, termed it ‘obstetrical acute yellow atrophy’; the condition has subsequently been grouped with acute fatty liver of pregnancy.

It can be shown that the hepatic alterations are dose-dependent. Patients with pyelonephritis exhibit a significantly decreased renal clearance of the drug. Upon this state of compromised renal function is then superimposed the renal toxicity of tetracycline. The adverse effect of tetracycline is manifested by:

(1) inability of the kidney to concentrate urine; and
(2) rising serum BUN and creatinine levels.

Not infrequently a concomitant feature of tetracycline hepatotoxicity is pancreatitis. Isolated pancreatitis has also been identified when a dose of only 1–2 g/day has been administered parenterally.

CHLORAMPHENICOL

Chloramphenicol is a very valuable drug. Yet because of the possibility of fatal drug-induced aplastic anemia, its clinical use should be restricted to potentially life-threatening situations that warrant the risk involved, and then only when the patient is under close hematologic supervision.

Chloramphenicol is capable of traversing the placental barrier. Studies in term infants reveal drug concentrations in the plasma that are between 30% and 80% of maternal concentrations. Despite the ability of chloramphenicol to interfere with the function of messenger RNA, no drug embryopathy has yet been attributed to its administration during gestation.

Once fetal viability is achieved, the existence of an acceptable alternative antibiotic is a relative contraindication to the use of chloramphenicol in the third trimester. Often maternal complications warranting its administration result in fetal death *in utero* or in premature termination of pregnancy. If premature birth occurs, because of transplacental transfer of the drug the fetus is exposed to an immediate risk from an adverse drug reaction. As long as the integrity of the maternofetal placental circulation is maintained the fetus is capable of drug equilibrium with the maternal host, and its capability to eliminate the drug and its metabolic products is not challenged.

The major mechanisms for the elimination of chloramphenicol from the body are:

(1) inactivation through conjugation with glucuronic acid; and
(2) excretion by (a) glomerular filtration of free chloramphenicol and (b) tubular excretion of the glucuronic acid conjugate.

Neonates, especially premature infants, when receiving large doses of the drug, have developed a clinical pattern which is termed the ‘gray baby syndrome’. Clinical deterioration due to chloramphenicol toxicity usually begins 4 days after therapy has started. Onset of toxicity can be influenced by the relative fetal immaturity or increasing drug dosage, or both. In the first 24 hours the infant vomits, suffers from irregular and rapid respiration, shows abdominal distention, and refuses to suck. Within the next 12–24 hours, the characteristic ashen discoloration (from which the syndrome derives its name), hypothermia, and flaccidity develop. These signs are followed shortly by neonatal demise

secondary to what has been interpreted as cardiovascular collapse. No characteristic pathologic changes attributable to the use of chloramphenicol are demonstrable in any organ system, including the hematopoietic system.

Chloramphenicol toxicity in the neonate is due to the free drug *per se* rather than to its metabolic products. Anuric patients receiving chloramphenicol develop extremely high circulating levels of the glucuronic form of the drug with no untoward effects. Similarly, the glucuronic acid amide metabolite recovered from the urine of infants appears to have little demonstrable toxicity.

The drug toxicity is a function of:

(1) the immaturity of the enzyme systems responsible for conjugation of the drug with glucuronic acid; and
(2) decreased renal clearance of the free form of the drug.

The quantity of hepatic glucuronyl transferase is diminished in the first 3–4 weeks of life. The quantitative inadequacy of this enzyme system is even greater in premature infants. In the newborn infant, glomerular filtration rates for insulin, mannitol, and creatinine are 30–50% of adult levels. This combination is responsible for increased circulating levels of free chloramphenicol and the resulting syndrome.

ERYTHROMYCIN

Five reports recently published have suggested maternal ingestion of erythromycin after the thirty-second week may lead to early onset infantile hypertrophic pyloric stenosis. Theoretically, macrolide antibiotics may interact with gastric motilin receptors causing strong gastric and pyloric bulb contractions resulting in pylorus hypertrophy

Cooper *et al.* conducted a retrospective cohort study utilizing Tennessee Medicaid prescription records linked to hospital discharge diagnosis and surgical procedure codes recorded on birth certificates. Of 260 799 mother/infant pairs studied, 13 146 had prescriptions for erythromycin and 621 received a non-erythromycin macrolide. The authors reported no association of infantile hypertrophic pyloric stenosis with *in utero* exposure to erythromycin in either late pregnancy or at any stage of gestation. A weak association of infantile hypertrophic pyloric stenosis with non-erythromycin macrolide was apparent but causal inference was limited by the small number (3 cases) of affected children.

Likewise, a surveillance study of 229 101 Michigan Medicaid recipients conducted between 1985 and 1992 reported that 6972 children had been subjected to erythromycin in the first trimester of pregnancy. Three hundred twenty (4.6%) were found to have major birth defects compared to an expected number of 297 (4.3%). These data do not support an association of erythromycin and congenital malformations.

Philipson *et al.* studied erythromycin in pregnant women between the 10th and 18th weeks and reported peak serum levels ranged from 0.29 to 7.2 μg/ml and that peak concentrations were achieved at 2 hours in seven of nine patients and at 4 hours in the remaining two patients. Both erythromycin base and estolate were used in the study. Forty percent of their subjects were ‘low absorbers’, defined by the authors as those whose peak serum levels were less than 20% of the arithmetic mean value for their group.

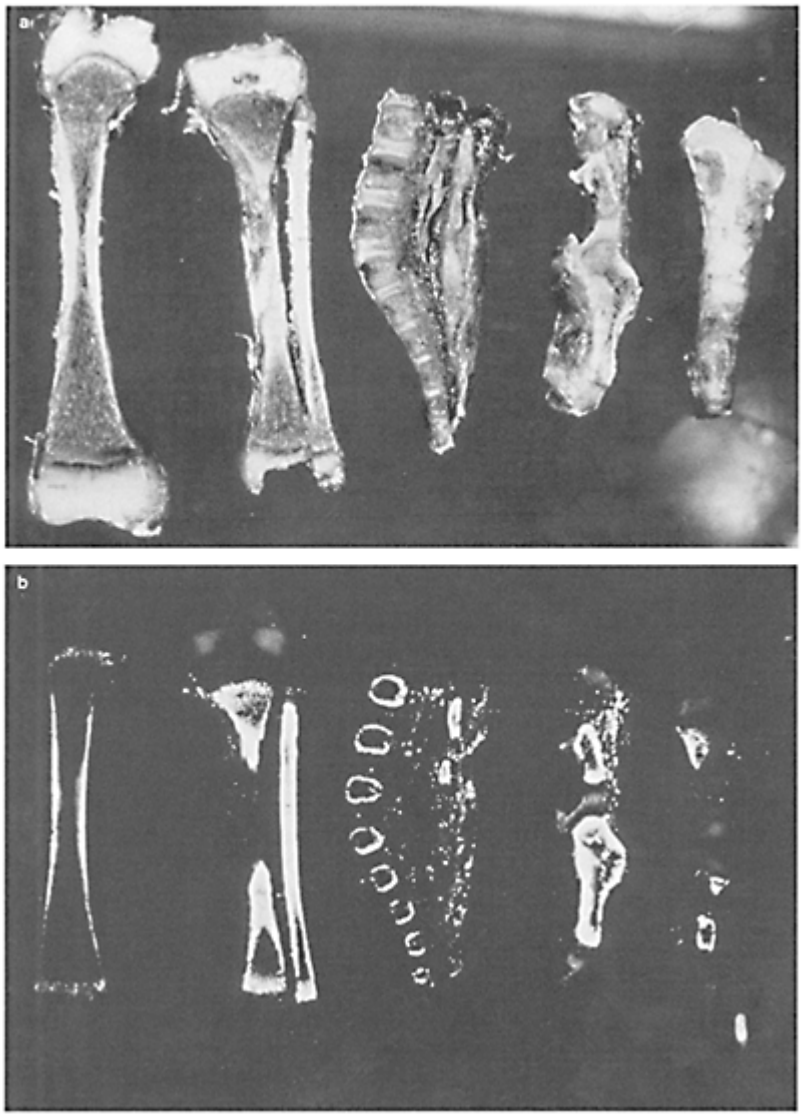

Figure 5.1 Representative bones of a 28-week-old fetus whose mother had received 23 g tetracycline during gestation. (a) Sagittal section. (b) Sagittal section demonstrating the amount of autofluorescence due to deposition of tetracycline

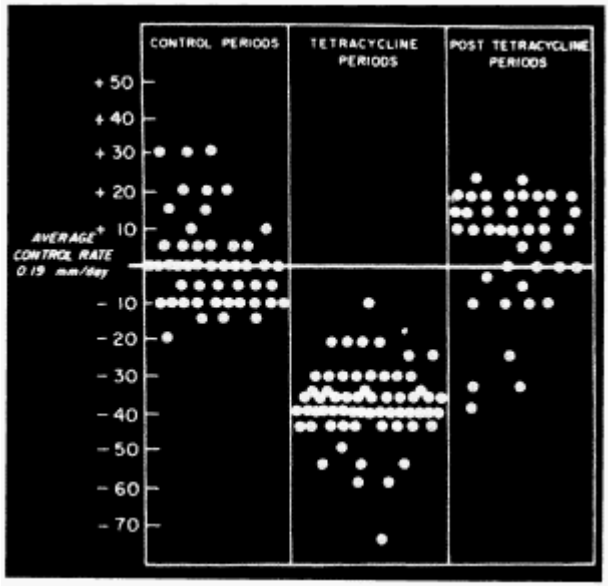

Figure 5.2 The control panel plots the percent deviation of each control fibula growth rate from the average control rate. Each white circle in the tetracycline and post-tetracycline panels represents the per cent deviation of each fibula growth rate as compared to the control rate

Using an identical protocol, Glover and Larsen studied the pharmacokinetics of erythromycin base in late pregnancy, of which seven of their 10 subjects were in the third trimester. Eight of the ten subjects achieved peak serum levels within 4 hours with individual concentrations ranging from 0 to 2.9 μg/ml. Two of the ten had no detectable serum levels of erythromycin by 4 hours, of which one required hospital admission for rehydration and was found to have a serum level of 0.6 μg/ml 3 hours after the 7th dose. These investigators reported serum levels to be lower than those of Philipson's study, with a mean serum level of 0.21±0.19 μg/ml, compared to Philipson's mean level of 4.1 μg/ml. While some patients have serum levels that reach the median minimal inhibitory concentration for such pathogens as *Neisseria gonorrhoeae* (0.1 μg/ml) and *Chlamydia trachomatis* (0.5 μg/ml), there remains a concern that patients who have no detectable levels, at least by 4 hours, are at risk for poor treatment outcomes. Additionally, such low maternal serum levels may limit fetal exposure to the drug.

FLUOROQUINOLONES

Fluoroquinolones are synthetic, broad-spectrum anti-infective agents used to treat urinary tract and other systemic infections. They have activity against most *Enterobacteriaceae, Pseudomonas, Klebsiella* and *Proteus* species as well as beta-lactamase producing strains of *N. gonorrhoeae*. Cipro® brand of ciprofloxacin is the most frequently prescribed member of these quinolone drugs. Data collected after introduction of these agents suggests an association of fluoroquinolones and cartilage defects in antibiotic-exposed infants may be a valid cause of concern. Although doses six times the usual daily human dose have not produced malformations in mice, rats and rabbits, multiple doses of fluoroquinolones have been associated with lesions of cartilage in weight-bearing joints of laboratory animals.

Seven reports have been published in recent years addressing fluoroquinolone therapy and congenital malformations. Pastuszak *et al.* reported on pregnancy outcome data of 134 women who received fluoroquinolones largely in the first trimester. Fluoroquinolone-exposed pregnancies were compared to matched controls. No significant differences were observed in spontaneous abortion, live births, fetal distress in labor or the cesarean section rate. The birth weights of the fluoroquinolone-exposed babies were 162 g higher than those of the control group.

Schaefer *et al.* reported data of 549 fluoroquinoloneexposed children of whom 509 were exposed to the drug during the first trimester of pregnancy. Twenty of these had congenital anomalies (4.9%). In the same report, 116 cases from the manufacturer's registry were discussed. Of these there were 91 live births, 15 elective terminations and 10 spontaneous abortions. Of note was that six of the 91 live births had congenital anomalies. However, the authors concluded the number of malformations observed did not exceed the expected rate of birth defects and that quinolone exposure in pregnancy is not an indication for elective termination. Evaluation of the collective anomalies reported from these seven reports fail to reveal a specific pattern of malformations in association with fluoroquinolone exposure. Nonetheless, until conclusive data is available, treatment with fluoroquinolones in pregnancy should be reserved for

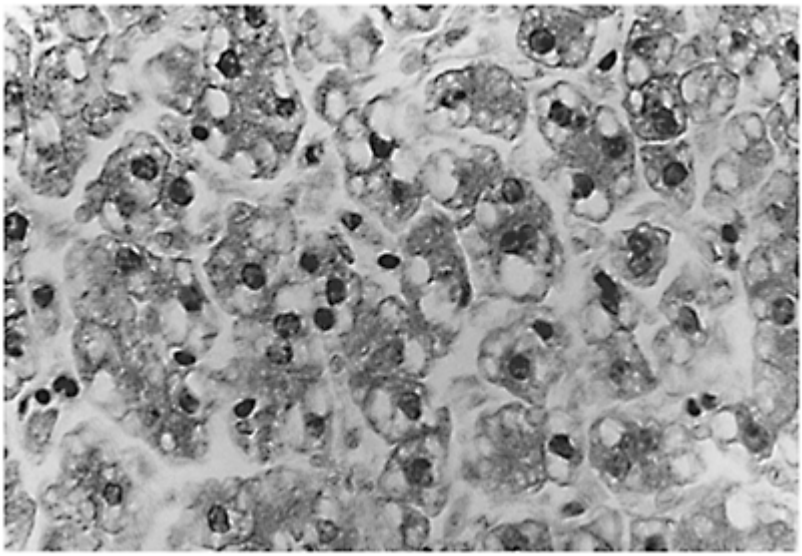

Figure 5.3 Multiple small intracytoplasmic lipid-laden vacuoles within hepatocytes in a patient with evidence of hepatocellular decompensation following 9 g tetracycline IV. (H&E, x270)

life-threatening infections that are unresponsive to other classes of antibiotic therapy.

ISONIAZID

The use of isoniazid is not undertaken without some trepidation. Garibaldi *et al.* reported 21 cases of hepatitis, two fatal, among 2300 government employees receiving isoniazid prophylaxis. Isoniazid hepatitis is an entity observed primarily in elderly females. Because of the tendency for any hepatotoxic drug to be potentiated by pregnancy, the Centers for Disease Control now recommend that pregnancy be considered a contraindication to the prophylactic use of isoniazid. A prodromal period marked by malaise, fatigue, and anorexia almost always precedes the appearance of jaundice. If isoniazid is stopped promptly a serious outcome can be avoided. The decision to administer or not administer isoniazid to a gravida should be individualized. If therapy is given, the patient should be monitored clinically and biochemically.

Isoniazid administration during gestation has been incriminated in the development of mental retardation and (rarely) convulsions and myoclonia in the progeny presumably due to the ability of its degradative products to interfere with the metabolism of pyridoxine. To counterbalance this possibility when isoniazid is administered during

pregnancy it is advocated that vitamin B12, 50 µg daily, be given for possible fetal as well as maternal indications. Although it has been suggested that therapy with bacteriostatic drugs, including isoniazid, for tuberculosis in pregnant women may increase the risk of congenitally defective infants two- or threefold, this hypothesis has yet to be confirmed.

STREPTOMYCIN

It has been shown that prolonged treatment with high doses of streptomycin during pregnancy may result in some degree of irreversible bilateral sensorineural hearing loss and vestibular damage. These effects are less common when the fetus is exposed to the drug after the fifth month of pregnancy. While the fetus is at risk, this appears to be a dose-related phenomenon. The existence of acceptable alternative forms of antituberculous therapy in pregnancy has relegated this form of drug toxicity to a phenomenon which reminds us that antibiotics cross the placenta. Miliary tuberculosis, tuberculosis meningitis, or a strain of tubercle bacillus resistant to most other drugs constitute the only indications for the use of streptomycin in pregnancy.

SULFONAMIDES

Sulfonamides administered during pregnancy equilibrate in maternal and fetal plasma within 3 hours. The plasma drug levels in the fetus are approximately 50–90% of those in the maternal plasma. This is dependent on the affinity of the sulfonamides for albumin, which differs considerably among the drugs in clinical use. Silverman and colleagues, in a control study of two prophylactic antibacterial regimens in the therapeutic management of premature infants, noted an unexpected increase in mortality in the group receiving penicillin and sulfisoxazole. At necropsy this group had kernicterus 10 times more frequently than those infants who received oxytetracycline. Most of the infants who died of kernicterus had shown bilirubin levels of less than 15 mg/100 ml.

It has subsequently been shown *in vitro* that sulfisoxazole successfully competes with bilirubin for binding sites on the serum albumin molecule. This competition of sulfonamides releases bilirubin from its protein-bound form and facilitates its diffusion into tissues and the development of kernicterus. The treatment of glucuronic transferase genetic-deficient rats with sulfonamides results in a marked increase in mortality despite low serum bilirubin concentrations. Just as the glucuronosyl transferase system is immature at birth, so is the acetylation mechanism which constitutes the alternative pathway for the detoxification of the sulfonamides.

The use of sulfonamides, especially the long acting forms, should be restricted in the 6 weeks prior to parturition. Maternal treatment with sulfonamides at the time of parturition may necessitate exchange transfusion therapy for the newborn infant.

TRIMETHOPRIM

Trimethoprim is a diaminopyrimidine which competitively antagonizes folic and folinic acids. Trimethoprim is available as a single agent and is utilized effectively with sulfamethoxazole (Septra®, Bactrim®) in the treatment of urinary tract infections. The antimicrobial activity of this combination results from its action on two steps of the enzymatic pathway for the synthesis of tetrahydrofolic acid. Recent reports suggest that trimethoprim use in the first trimester may result in anatomic defects. A woman who was dieting in early pregnancy was treated for 10 days with a combination of trimethoprim-sulfamethoxazole for acute otitis media beginning in the third menstrual week. Dimenhydrinate was added as an antiemetic at the seventh week for hyperemesis. At 38 weeks she delivered a 3225 g infant with lobar holoprosencephaly that included a median cleft lip and palate, a flat nose without nostrils, hypoplasia of the optic discs, a single ventricle and fused thalami in the midline.

Richardson *et al*. have reported neural tube defects that occurred in the pregnancies of two HIV-infected women who received trimethoprim-sulfamethoxazole combination therapy for prophylaxis against *Pneumocystis carinii* concurrently with zidovudine and zalcitabine. Subsequently folic acid was added but the date of initiation is in question. At term the woman delivered a female infant with an anomaly of the first lumbar vertebra and a protrusion of the second lumbar vertebra into the spinal cord. The other HIV-infected woman was taking trimethoprim-sulfamethoxazole at the booking visit (15 weeks), along with didanosine, stavudine, nevirapine, and a multivitamin that were prescribed prior to conception. Anatomic survey via ultrasonography at 19 weeks gestation revealed spina bifida and ventriculomegaly. The pregnancy was terminated and at necropsy the fetus was found to have Arnold-Chiari malformation, ventriculomegaly, sacral spina bifida, and a lumbosacral meningomyelocele.

In a report from a multi-center case-control surveillance survey conducted in 80 maternity or tertiary care hospitals in the US and Canada, the effects of exposure to folic acid antagonists on embryo and fetal development were evaluated. Folic acid antagonists were classified as follows: Group 1. dihydrofolate reductase inhibitors (methotrexate, aminopterin, sulfasalazine, pyrimethamine, triamterene and trimethoprim. Group 2. drugs that affect other enzymes in folate metabolism, increase the metabolism of folate (phenobarbital, phenytoin, primidone, carbamazepine), and interfere with the absorption of folate. None of the controls took folic acid antagonists. Exclusions included infants with defects associated with a syndrome and those with neural tube defects. Analysis for trimethoprim exposure resulted in a relative risk of 4.2. These data appear to confirm that trimethoprim is a low level teratogen.

MISCELLANEOUS DRUGS

Ethionamide, pyrimethamine, and rifampin are in the category of drugs for which teratogenicity has been postulated or demonstrated in animal model systems.

Ethionamide, a drug used in the treatment of persistent tuberculosis, is potentially teratogenic and its use is contraindicated in pregnancy. In a 2000 report of 23 ethionamide-exposed infants, seven were found to have anomalies, including two with 21 trisomy syndrome.

Pyrimethamine is a diaminopyrimidine which competitively antagonizes folic and folinic acids. Pyrimethamine (Daraprim®), in combination with a sulfonamide, has been used in the treatment of toxoplasmosis and some sensitive and multi-resistant strains of *Plasmodium falciparum*. The mechanism of action is similar to that observed with trimethoprim and sulfamethoxazole in combination, namely, a sequential block resulting in an additive synergistic effect. This drug is a potential teratogen in experimental animals and must be used with great caution in pregnant patients.

Rifampin is a valuable second-line antituberculous drug used in the treatment of drug-resistant strains of *Mycobacterium tuberculosis* and atypical mycobacterial infection. Although no teratogenicity has been documented, its ability to inhibit DNA-dependent RNA polymerase contraindicates its use during pregnancy.

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6
Timing of antibiotic therapy

FEVER

Fever has been the traditional early warning system for the physician for indicating the development of infectious complications as well as primary disease.

WHAT CONSTITUTES AN ABNORMAL TEMPERATURE

Any temperature greater than or equal to 38 degrees Celsius is abnormal. Any range of temperature between 37.6 and 37.9ºC is called the GRAY ZONE. It is a mandate, not for action but for concern. Should an abnormal temperature develop from a set of temperatures which have been in the GRAY ZONE, the probability of infection is great.

When monitoring a patient at high risk for an infectious complication, early morning temperatures before breakfast often are harbingers of the subsequent temperature patterns. If it is elevated above the anticipated baseline, the patient's temperature will probably spike in the late afternoon. The best medicine that can be practiced is preventive medicine; the next best is early intervention.

A significant number of patients with endomyometritis following cesarean section will have very minimal localized findings. Most patients have a significant amount of inflammatory induration involving the vaginal cuff following vaginal hysterectomy. Temperature elevations are often a mandate to an aggressive fever work-up. In the absence of a demonstrable nongenital cause for the fever, a commitment to exclude operative site disease is implemented. The following criteria have been derived primarily from patients with endomyometritis following cesarean section; however, they have proven to be highly adaptive for the majority of postoperative infectious complications.

(1) **Any temperature greater than or equal to 38.6°C.**
Obtain an immediate second reading, and if it confirms the validity of the initial reading, institute an immediate fever work-up.

(2) **Any two (2) temperatures equal to 38°C or greater taken four (4) hours apart for which the second temperature is more than 0.2° higher than the first.**

(3) **Three (3) temperatures equal to 38°C or greater in any 24 hour period. The significance of temperature is in the first 24 hours postoperatively.**

The standard definition of the American College of Obstetricians and Gynecologists disregards the validity of relatively minor temperature elevation in the first 24 hours (less than 38.6°C). These elevations are frequently attributed to postoperative atelectasis, urinary tract infection, and in postpartum patients, breast engorgement. Unless associated with aspiration, atelectasis is not a cause of fever. One can tie off a bronchus and not

induce fever. The incidence of postoperative atelectasis in most oncology patients undergoing radical surgery documented by serial blood gases approaches 100%. Up to 20% of patients will have some roentgeno-graphic evidence of atelectasis, yet the incidence of fever in this group is remarkably low in the first 24 hours. Finding greater than 100000 colonies per ml of a single bacterial species in a urine specimen documents the presence of asymptomatic bacteriuria. Unless costovertebral angle (CVA) tenderness or severe suprapubic and/or back pain is present, urinary tract infections are not a cause of fever.

When seeking an etiology for the development of febrile morbidity following an operative procedure, homage should be paid to Willie Sutton's First Law: **Go where the gold is**. Make a working hypothesis of operative site infection and then try to PROVE IT WRONG.

ANTICIPATED THE RAPEUTIC RESPONSE

When dealing with monoetiological disease due to *Neisseria gonorrhoeae* or *Streptococcus pneumoniae* pneumonia, the response is often dramatic. The precipitous drop in temperature in response to appropriate antibiotic therapy is termed a monoetiological response. If the organ system in which disease occurs is prone to compartmentalization with varying patterns of perfusion, i.e. the kidney, the probability of seeing a monoetiological curve is diminished. Most postoperative infections in Obstetrics and Gynecology are due to polymicrobial infection. With appropriate therapy, the time interval tends to be prolonged owing to the superimposition of multiple kill curves. Irrespective of whether one is dealing with monoetiological or polymicrobial therapy, the **anticipated therapeutic result** is the same. The patient should be **afebrile within 24–36 hours**. As long as each succeeding temperature is lower than the preceding temperature but is above 38.6ºC, one can still maintain a valid commitment to the antibiotic regimen utilized. Similarly, if after 12 hours of antibiotic therapy the patient's temperature continues to rise, it is unlikely the patient will profit from 12 more hours of the same therapy. If a patient is not responding within 24 hours, one should question the validity of either the initial diagnosis or the antibiotic therapy—a patient whose temperature comes down slowly over four or five days is a patient who is CURING HERSELF. The initial antibiotic has contributed to her recovery by eliminating part of the bacterial flora which could potentiate the infectious morbidity, but unless disease involves a site where bioavailability of antibiotic is a problem, the continued administration of antibiotics beyond five days is more for the physician's well-being than the patient's. If the patient is not responding to antibiotic therapy after 48 hours, both the patient and the physician have a problem.

ANTIBIOTIC ADMINISTRATION

The maximum dosage which can be safely administered should be given in the first 24 hours and thereafter be cut back or tapered to the minimum dose unless there is a problem of bioavailability of drug, i.e. meningitis, septic arthritis, abscess formation, or

reticuloendothelial intracellular sites of bacterial replication. In the majority of instances, **the battle is usually won or lost in the first 24 hours**. If won, subsequent drug administration is more medicolegal than therapeutic. If lost, the patient needs appropriate therapy, not more of the same. If infectious complications develop following the preoperative administration of an antibiotic, the use of an antibiotic with the same spectrum of coverage is not recommended.

WHEN TO DISCONTINUE PARENTERAL ANTIBIOTICS

The initial commitment to parenteral administration of antibiotics for hospitalized patients is totally warranted. The basic question is how long do you sustain this commitment? The decision as to when to discontinue parenteral antibiotic for oral administration is one which requires a great deal of individualization. Conversion from intravenous to oral mode of antibiotic administration should be done 24 hours after evidence of resolution of infectious complication unless contraindicated by ileus, intestinal hypermotility, etc. Most patients can be converted to oral antibiotics within 24 hours after resolution of all evidence of infectious morbidity.

Early conversion to oral antibiotics reduces intravenous catheter-induced or related morbidity. Parenteral antibiotics cost seven to 10 times what the equivalent dose of oral medication costs.

7
Antibiotic induced diarrhea

Pseudomembranous enterocolitis (PME) is the consequence of a filterable, heat-labile enterotoxin elaborated by selected strains of *Clostridium difficile*. In selected cases, the antibiotic in question eradicates that portion of the gastrointestinal tract flora that suppresses the growth of *C. difficile.* The loss of bacterial interference permits the resistant *C. difficle* to numerically partially fill the biologic void created, and in so doing elaborate the exotoxins. A single dose of an antibiotic given for cesarean section prophylaxis is capable of inducing disease. Privitera *et al.* studied *C. difficile* intestinal colonization following a single two gram intravenous dose of either a cephalosporin or mezlocillin. *C. difficile* was detected in 23% of patients who had received a cephalosporin, in 3.3% of patients given mezlocillin and in none of the 15 controls given no antibiotics.

The probability of PME appears to be partially influenced by the route of antibiotic administration. This is particularly true of clindamycin. The incidence of this complication is significantly more frequent with per oral as opposed to parenteral administration.

The clinical manifestations of antibiotic induced diarrhea are quite variable, running a spectrum from mild, nuisance diarrhea which resolves spontaneously to severe infections characterized by pseudomembranous colitis, toxic megacolon, or colonic perforation. In approximately 30% of cases, symptoms develop as late as several weeks after discontinuation of antibiotics.

A large number of antibiotics have functioned as inciting drugs for PME (Table 7.1). Antibiotics with significant activity against anaerobic bacteria alter the gut microbial ecosystem and put the patient at greater risk for antibiotic induced diarrhea. The use of multiple antimicrobial agents as well as more prolonged course of therapy further increases the potential of *C. difficle* colitis. Initial symptomatology is simply that of an increased number of bowel movements (diarrheal syndrome). Symptoms of PME include cramping, hypogastric pain, profuse watery diarrhea (often with occult blood), and fever, usually not exceeding 38.9ºC, in addition to small-bowel diarrhea. Symptoms usually evolve within three to nine days after antibiotic therapy is started. Definitive diagnosis of pseudomembranous colitis is made by proctoscopy. Raised, plaque-like pseudomembranes associated with erythema and edema are diagnostic of disease, with the degree depending on the severity of involvement (Figure 7.1). Patients with diarrhea without pseudomembranes will exhibit only minimal edema without much overt inflammation.

Table 7.1 Drugs with potential for pseudomembranous enterocolitis (PME)

Level I: Antibiotics commonly associated with PME
Penicillin, penicillin/beta-lactamase inhibitors, cephalosporins, and clindamycin
Level II: Antibiotics and drugs associated with PME
Antibiotics: Chloramphenicol, erythromycin, lincomycin, imipenem-cilastatin, quinolones, rifampin, tetracycline, trimethoprim-sulfamethoxazole. Antineoplastics: doxorubicin, cisplatin, cyclophosphamide, fluorouracil, methotrexate
Level III: Antibiotics rarely associated with PME
Aminoglycosides, metronidazole, vancomycin.

Regardless of which condition is present, antibiotic therapy should be immediately discontinued. If antibiotic therapy is continued in a patient with pseudomembranous colitis, the proctoscopic findings become worse; the plaques gradually enlarge and coalesce. In the diarrheal syndrome there is prompt amelioration of symptoms with the cessation of drug therapy. Patients with pseudomembranous colitis may continue to have multiple bowel movements for two to three weeks

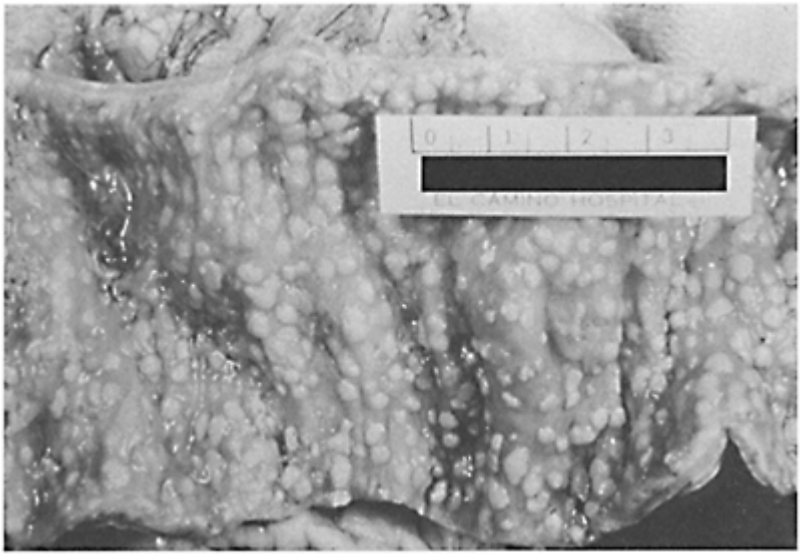

Figure 7.1 Raised plaque-like pseudomembranes in the colon of a patient who died with clindamycin-induced enterocolitis. (Courtesy of S.Kabins, MD, Chicago, IL)

following discontinuation of therapy. In general, the longer the drug is given to patients with pseudomembranous colitis, the more prolonged the diarrhea is and the longer the proctoscopic examination is abnormal. In the absence of aggressive therapy, PME may progress to toxic megacolon, perforation of the bowel wall, peritonitis, and endotoxic shock.

DIAGNOSIS

Any patient who develops three or more uniform stools per day for at least two days in the setting of exposure to antimicrobial or antineoplastic agents can be considered to have antibiotic associated diarrhea. Except in critically ill patients, laboratory evaluation is the principal diagnostic approach. Enzyme immunoassay detects the presence of toxins A or B in stool filtrates and is a rapid technique for diagnosing *C. difficile* infection. Polymerase chain reaction detects toxigenic *C. difficile* by amplification of the toxin A or B gene or both genes. The cytotoxin assay detects toxin B in stool filtrates by observing the characteristic cytotoxin changes that this toxin produces in standardized tissue culture cell lines.

A correctly performed stool culture is extremely sensitive in detecting the presence of *C. difficile*. Recovery of the organism from stool culture does not necessarily document causability. Up to 25–60% of hospitalized patients, 10–25% of infants and 3% of the general population in the United States are asymptomatic carriers of *C. difficile*. Not all strains of *C. difficile* are toxigenic. Definite diagnosis necessitates the identification of *C. difficile* toxin in the stool.

Patients who develop symptoms several days after completion of antibiotic therapy are at much higher risk of having antibiotic associated diarrhea than nonspecific diarrhea. Individuals with a prior history of antibiotic associated diarrhea who again develop diarrhea are likely to be infected with *C. difficile*. For those two categories of patients, empiric therapy with metronidazole or vancomycin should be considered while the cause of the diarrhea is being determined.

Table 7.2 Protocol for patients developing diarrhea while on antibiotics

1. A. Discontinue antibiotics immediately
   B. Obtain electrolyte values
   C. Correct any electrolyte abnormality while carefully restoring intravascular volume
   D. Pepto Bismol can be given, but avoid antiperistaltic drugs.
2. If diarrhea stops within 24 hours, there is no need to institute further therapy.
3. If diarrhea persists, examine patient with a proctosigmoidoscope. If raised yellowish-white plaques 2–5 mm in size superimposed on edematous colonic mucosa are identified, the patient has pseudomembranous enterocolitis—put the bowel to rest and obtain consultation from GI Medicine.

Table 7.3 Therapy for pseudomembranous enterocolitis

Regimen of choice
Vancomycin: oral, 125–500 mg qid for 10 days
Metronidazole: oral, 500 mg tid or 250 mg qid for 10 days
Alternate regimen
Bacitracin*: oral, 25 000 units qid for 10 days

*Bacitracin therapy has an inferior cure and relapse rate and should not be used as initial therapy; tid, three times a day; qid, four times a day

THERAPY

Whenever a patient is placed on antibiotic therapy, logging of a daily stool count is recommended. When the number of bowel movements increases to three per day for two days, antibiotic therapy should be discontinued.

If a patient develops diarrhea while on an antibiotic, discontinue the antibiotic immediately (Table 7.2). Obtain electrolyte evaluations and correct any electrolyte abnormalities while carefully restoring the intravascular volume. If the diarrhea stops within 48 hours, there is no need for further evaluation. If diarrhea persists or other symptoms consistent with disease are present, the patient needs to be staged by proctoscopy. Once PME is documented, oral therapy is indicated.

Vancomycin is expensive but is still the treatment of choice for severe PME (Table 7.3). Metronidazole and bacitracin are less expensive alternatives for treating mild cases when concern for vancomycin resistance takes precedence.

Vancomycin is given orally in doses of 125 mg four times daily for ten days. This is directed against the etiologic agent. The drug must be given orally to provide high colonic levels. Once the drug is stopped, a high percentage of patients relapse with a recurrence of symptoms associated with reappearance of *C. difficile* toxin in the stool.

Metronidazole in a single 1.5 g per day dose for 10 days has achieved cure rates of 92–95%. However, this drug has been implicated as the precipitating agent for rare cases of antibiotic-associated colitis.

Approximately 8 to 20% of patients treated will experience a relapse. These individuals tend to be older and have had a higher frequency of recent surgery than those that did not relapse. Relapses are usually due to the persistence of antibiotic-resistant *C. difficile* spores rather than the development of antibiotic resistance by the vegetative organism. In patients with relapses, retreatment with the initial antibiotic achieves a greater than 90% cure rate. The emergence of vancomycin resistant enterococci and staphylococci may influence drug therapy for antibiotic associated diarrhea. In the absence of significant disease, metronidazole may be the agent of choice.

NOSOCOMIAL COLONIZATION

Colonization and subsequent disease due to *C. difficile* is a potential nosocomial problem. When a nosocomial outbreak occurs, identification of asymptomatic carriers and their treatment with metronidazole have been effective in aborting the outbreak. A heightened awareness of possible nosocomial transmission within intensive care units is necessary to prevent or arrest future clusters of cases. The diagnosis of one patient with this infection in a unit should prompt a review of all other patients within the unit.

Enteric infection control procedures including isolation of infected patients and frequent hand washing are additional, important measures which should be taken to minimize the development and spread of this nosocomial infection.

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8
Prophylactic antibiotics

In women undergoing abdominal surgical procedures, the prophylactic administration of any antibiotic which is effective against the predominantly Gram-positive spectrum will reduce in a statistically significant manner infectious morbidity in the postoperative period. A reduction in severe infection parallels the overall reduction of infectious morbidity; however, the incidence never becomes zero.

GROUND RULES FOR ANTIBIOTIC PROPHYLAXIS

Six guidelines governing the prophylactic use of antibiotics in obstetrical surgery were developed by Ledger:

(1) Limit antibiotic use to a high-risk situation.
(2) Establish tissue levels of the antibiotic before the incision.
(3) Give a short course of therapy to minimize dose-related adverse drug reactions.
(4) Use second- or third-line antibiotics.
(5) Choose antibiotics that are effective against the anticipated pathogenic spectrum.
(6) Be sure that benefits outweigh the possibility of an adverse drug reaction.

Limiting use to a high-risk situation

The purpose of prophylactic antibiotics is to avert the serious infections which may intervene. Women with antedating problems (chronic cervicitis, repeated episodes of sexually transmitted disease with or without structural damage) abnormal vaginal flora (bacterial vaginosis (BR) or bacterial excess syndrome (BES)) and individuals in whom hemostasis will be difficult to obtain for physiologic or anatomic reasons, or in whom surgery is anticipated to be difficult, are at augmented risk.

The need to establish tissue levels of the antibiotic before incision

The theoretical basis for this guideline emanates from the experiments of Miles and Miles and their subsequent reduplication a decade later by Burke. Both sets of investigators demonstrated in animal model systems that antibiotics administered before or simultaneously with local challenge with bacteria susceptible to the selected antibiotic were highly effective in aborting the infectious disease, whereas if the antibiotic was given as late as four hours after the microbes had been inoculated, it was essentially worthless. This preoperative interim has been called the ‘decisive period’. While this concept is probably valid in selected instances (e.g. for the orthopedic surgeon doing a total hip replacement who is concerned with coagulase-negative staphylococci), it is

probably not as valid for vaginal hysterectomies. Postoperative infection, in these circumstances, is due to a polymicrobial infection. Consequently, antibiotic administration beyond the 'decisive period' will be relatively effective. Rather than precluding initiation of the anaerobic progression, it would interrupt it prior to the induction of disease.

Minimizing dose-related adverse reactions

The concept of minimizing the duration of therapy in order to minimize dose-related adverse reactions is endorsed in all situations in which antibiotics are administered prophylactically. It is probable that one can achieve a statistically comparable effect on the incidence of disease following cesarean section with a single bolus administration of an appropriate antibiotic as has been achieved with three dose, three day and five day regimens. There is no rationale for prolonged administration.

Use of a second- or third-line antibiotic

The goal in this instance is to minimize the emergence of strains that are resistant to the antibiotic in question. Cephalosporins, being second-line antibiotics and having little applicability in the practice of obstetrics and gynecology, fit this guideline ideally.

Antibiotics for the anticipated pathogens

What is achieved with the cephalosporins is the eradication of the minor constituents of the vaginal flora—corynebacteria, propionibacteria, lactobacilli, *Gardnerella vaginalis*, coagulase-negative staphylococci, viridans streptococci, some of the *Enterobacteriaceae*, etc.—leaving behind the enterococci, the cephalosporin-resistant *Enterobacteriaceae*, and the penicillin-resistant *Bacteroidaceae*. The cephalosporins do not effectively cover the anticipated pathogenic spectrum.

Benefits must outweigh the possibility of a reaction

The potential for adverse drug reactions must be considerably less than the risk of postoperative infection when an antibiotic is given prophylactically. There must be a careful balancing of risks and benefits. The cephalosporins have been responsible for at least two surgical deaths due to anaphylaxis in cases in which the drugs were used prophylactically.

MECHANISM OF ACTION OF PROPHYLACTIC ANTIBIOTICS

Qualitative bacteriologic studies of women undergoing vaginal hysterectomy have shown that there are alterations of the bacteriologic flora as a consequence of the operative procedure which occur independent of the selective influences of antibiotics. Only very rarely do preoperative antibiotics 'sterilize' the posterior vaginal pool with any degree of regularity. Subsequent quantitative bacteriologic studies have shown that the reductions

achieved in the total aerobic and anaerobic counts are transient. Postoperatively, the total aerobic and anaerobic counts approximate or exceed those obtained in the preoperative period. Prophylactic antibiotics eradicate selective constituents of the vaginal flora. The bacteria which have been eliminated are not usually considered to have pathogenic significance. After the prophylactic administration of a semisynthetic penicillin or a cephalosporin, the penicillin-resistant *Bacteroidaceae* including *Bacteroides fragilis, Prevotella* species, members of the *Enterobacteriaceae,* and the enterococci emerge as the dominant constituents of the vaginal flora. In short, we eradicate the nonpathogenic bacteria and leave behind the endogenous organisms which have a recognized capacity to function as prime pathogens.

The obvious question is 'Why then do prophylactic antibiotics work?' The answer appears to be that they interrupt the potential for the anaerobic progression. They eradicate the 'facilitating flora' which may transform the microbiologic environment into one conducive for the replication of obligate anaerobes. Tangible evidence supporting this thesis has been gleaned by various investigators. Using meticulous surgical techniques and suction drainage they were able to achieve results comparable to those observed with prophylactic antibiotics. The presumed reasons have to do with the understanding of the pathogenesis of anaerobic infection. Being gentle with tissue, practicing good hemostasis, using small clamps to minimize the amount of crush injury, and removing all foreign bodies, minimizes the creation of a microbiologic environment in which the oxidation-reduction potential is conducive to anaerobic infection. The use of T-tube drainage demonstrated that, after iatrogenically creating a microbiologic environment which will select for the anaerobic progression, mechanically removing it can circumvent the ensuing infectious morbidity. The studies on prophylactic antibiotics seem to corroborate this thesis. When Swartz attempted to use prophylactic antibiotics in conjunction with T-tube drainage, he was unable to alter his percentages in a statistically significant manner. This observation implies that both T-tube drainage and prophylactic antibiotics operate on the same mechanism, though presumably at different points.

PERIOPERATIVE ANTIBIOTICS TO PREVENT POSTPARTUM ENDOMETRITIS FOLLOWING CESAREAN SECTION

Prior to 1974, infections were the second leading cause of mortality in women undergoing cesarean section. The therapeutic efficacy of perioperative antibiotics in preventing postoperative infectious complications in patients undergoing vaginal hysterectomy prompted the clinical application of this concept to patients undergoing cesarean section. As in the case of patients undergoing vaginal hysterectomy, a statistically significant reduction in operative site infectious morbidity can be demonstrated. Almost irrespective of the previous incidence of postcesarean endometritis, perioperative antibiotics will reduce the figure by at least 50%.

Not all women undergoing cesarean section are at equal risk for the development of postoperative endometritis. The risk of infection following cesarean section is markedly influenced by the socio-economic status of the woman, duration of labor, prolonged rupture of the fetal membrances and/or labor, presence of an abnormal endogenous

vaginal flora, presence of asymptomatic bacteriuria or known pathogen within the vaginal flora, presence of asymptomatic bacteriuria, and the operative skills of the surgeon.

Prior to the utilization of preoperative antibiotics, the incidence of endometritis following cesarean section varied between 35% and 60% in teaching hospitals as contrasted to private institutions in which the incidence of infection was usually below 20%.

Once a patient is designated as being at augmented risk, the selection of antibiotic and the time of its administration should be cost-effective for the patient and selected to minimize potential effects on the bacterial flora of the newborn and neonatal intensive care nurseries.

The need to establish effective antibiotic concentration within tissues prior to making the initial incision is paramount to its effectiveness. Classen *et al.* observed a greater than seven-fold increase when prophylactic antibiotics were administered greater than two hours before the operation when compared with cases in which drug administration occurred within the currently designated two hour period. The use of perioperative antibiotics in women at the time of parturition differs from that in women undergoing vaginal or abdominal hysterectomy in that the physician treating a woman at the time of parturition is treating not one but rather two biologically unique individuals. All antibiotics, to one degree or another, traverse the placental barrier so that invariably a neonate whose mother was treated with antibiotics during parturition would be sent to the newborn nursery with a serum antibiotic level that in time could influence the composition of the bacterial flora of the newborn and neonatal intensive care nursery. The impact on the bacterial flora probably would not be significant if the antibiotic utilized had a limited spectrum of susceptibility that was restricted to the Gram-positive bacteria; however, the cephalosporins, because of their efficacy against selected members of the *Enterobacteriaceae,* theoretically could adversely influence the constituency of aerobic Gram-negative bacterial flora. The first generation cephalosporins do not penetrate the placental barrier well; consequently, suboptimal levels in newborn serum and amniotic fluid are achieved. Repetitive exposure to suboptimal concentrations of an antibiotic is a recognized mechanism for the *in vitro* induction of antibiotic resistance.

Clinical studies have demonstrated that the endogenous bacteria that cause postpartum endometritis could often be demonstrated in amniotic fluid at the time of cesarean section. If bacterial access to the endometrial cavity prior to parturition is a major factor that selects for disease, those factors that enhance bacterial access prior to parturition should be associated with an increased incidence of endometritis following cesarean section. The incidence of disease is significantly augmented for gravida who are in active labor or who experience prolonged rupture of the fetal membranes in contradistinction to patients who undergo elective cesarean section.

The work of Burke was done in a closed animal system employing a single pathogen *(Staphylococcus aureus).* The postpartum endometrial cavity is an open system with physical continuity with the endocervical and vaginal bacterial flora. Disease is usually the consequence of polymicrobial infection. The mechanism by which perioperative antibiotics aborted infection in the animal model system of Burke is eradication of the causative agent. The mechanism by which antibiotics decrease the incidence of postcesarean endometritis is by eradicating the so-called facilitating flora, the bacteria within the vagina, which can further alter the oxidation-reduction potential of the

microbiologic environments to that point where no further lowering of the oxidation-reduction potential is required to ensure the replication of a single anaerobic genus of bacteria. A number of studies have demonstrated comparable efficacy between preoperative and postoperative administration of antibiotics.

The drug advocated by the author to avert infectious morbidity following cesarean section is ampicillin. The reasons for its selection are its cost, spectrum of coverage, bioavailability in amniotic fluid, and ability to be integrated into the concept of triple therapy should infectious complications develop in the postpartum period. If endomyometritis does develop, it is not necessary to restart ampicillin. The existing gaps in the Gainesville Classification can be closed with clindamycin or metronidazole and an aminoglycoside, thus achieving the coverage of triple therapy. Ampicillin should be administered when the decision is made to commit to abdominal delivery and continued until parturition has been achieved plus one dose. Not waiting until the cord is clamped will favorably impact on the incidence of perinatal septicemia. Three decades of abuse of ampicillin in the neonatal intensive care units has not significantly altered its spectrum of efficacy.

If a cephalosporin is used for prophylaxis, administration of the drug needs to be delayed until the umbilical cord is clamped. If a maternal infectious complication does ensue after cesarean section, the addition of clindamycin or metronidazole and an aminoglycoside will not achieve triple therapy equivalent. A gap will still exist for the enterococci (Category III).

PERIOPERATIVE ANTIBIOTICS TO PREVENT POSTOPERATIVE INFECTIONS FOLLOWING GYNECOLOGICAL SURGERY

The ground rules governing antibiotic prophylaxis for gynecologic surgery have been slower in evolution and modified by additional risk factors. While obstetrical surgery deals primarily with community-related bacteria in basically healthy individuals, gynecological surgery has a greater tendency to involve a hospital-modified bacterial spectrum in an older, sicker population. Factors predisposing the risk of postoperative infection in gynecological patients include:

(1) a hospital stay ≥72 hours prior to surgery;
(2) preoperative exposure to antibiotics;
(3) concomitant presence of disease; affecting small blood vessels, e.g. diabetes mellitus, irradication, collagen vascular disease, hypertension;
(4) obesity.

Classically, antibiotic prophylaxis is advocated when the procedure is associated with a significant risk of postoperative infection. The antibiotic chosen is required to:

(1) impact on a significant portion of the bacteria which, through the anaerobic progression or individually, can cause disease and have been shown to be effective in clinical trials;
(2) have an antibiotic half-life such that peak serum and tissue concentrations are functioning at the time of the operative procedure;

(3) not be associated with significant adverse drug reactions;
(4) should be effective when given in a single dose and the dose-cost should be relatively inexpensive.

The list of antibiotics which have been shown efficacious in prevention of infectious complications following gynecological surgery has been engendered by commercial rather than scientific interests. Unlike antibiotic prophylaxis for obstetrical infection where there is no statistical significance between disease avoidance with the first, second, or third generation cephalosporins, a closer probability of achieving statistical significance does occur with the broader spectrum antibiotic for gynecological procedures. The problem with most studies of efficacy is their inability to control

Table 8.1 Gynecological surgical procedures for which antibiotic prophylaxis is advocated

Abdominal hysterectomies
Pregnancy termination*
Radical hysterectomy
Vaginal hysterectomy

*see Chapter 64: *Infectious Complications Associated with Legal Termination of Pregnancy*

for operative variables such as duration of procedure, operative skill, blood loss, meticulous tissue handling techniques, etc. The operations for which antibiotic prophylaxis is advocated are listed in Table 8.1.

For relative simple gynecological surgery, single dose cephalosporin prophylaxis is still the standard of care, however when extensive surgery is contemplated, ampicillin/sulbactam combination has had the lowest incidence of postoperative wood infections.

Clinical studies have shown no value in continuing antimicrobial therapy beyond 24 hours in clean/ contaminated surgery. Prolonged use of antibiotics on dirty procedures is considered therapy and not prophylaxis.

Once an antibiotic has been given and an infectious operative site complication ensues, avoid restarting that or any close-related (in terms of spectrum of efficacy antibiotics) antibiotic.

FAILURE TO USE PROPHYLACTIC ANTIBIOTICS PROPERLY

Antibiotic prophylaxis requires proper case selection, use of an effective drug, proper dosage, proper route of administration, timing of administration and intraoperative dosing for operations over two hours. The Health Care Quality Improvement Project of New York State reported that 27%-54% of all patients did not receive antimicrobial prophylaxis in a proper or timely fashion. The principal misuse of prophylactic antibiotics involved duration of administration, timing of administration and intraoperative dosing. Premature administration was most frequent for operations that

occurred later in the day. Matuschka *et al.* have advocated administration of preoperative antibiotics in the operating room.

ANTIBIOTIC PROPHYLAXIS FOR INDUCED ABORTIONS

Periabortal antibiotic prophylaxis has been found to significantly reduce postabortal infections in women undergoing elective first trimester vacuum abortions. In a meta-analysis comprising over 5000 women, Sawaya *et al.* found an overall 42% decrease in interferon after analyzing results from 12 randomized trials. The American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynaecologists currently recommend the use of antibiotic prophylaxis at the time of induced abortions.

The questions which remain partially unanswered are which antibiotics and how long antibiotic prophylaxis should be carried out. Lichtenberg *et al.* surveyed practice patterns among member facilities of the National Abortion Federation. Eighty-one percent of respondents used doxycycline. A one-week regiment of doxycycline was the most commonly chosen. Shorter courses of oral doxycycline have no adverse affect on the incidence of ensuing disease.

The duration of antibiotic prophylaxis is partially determined by the population being served. The overall protective effect of antibiotic prophylaxis is most significant in women who have the high-risk criteria for possible chlamydial infections. The duration of antibiotic administration is that which would minimally eradicate an underlying chlamydial infection.

Penney *et al.* have reported that a strategy of universal prophylaxis is at least as effective in preventing postabortal infection as a screen-and-treat strategy for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Women with a single known partner or who have been recently tested for sexually transmitted disease can be prophylaxed with regimens as short as one day.

ANTIBIOTIC PROPHYLAXIS FOR PRETERM LABOR

A significant literature exists dealing with the use of prophylactic antibiotics in patients with preterm labor. In this clinical setting, antibiotic administration is hypothesized to delay or prevent preterm delivery. The underlying suppositions are that either women with preterm labor have an occult intrauterine infection or cervical/vaginal infection has initiated the prostaglandin cascade which initiated labor.

In support of the former postulate is the ability of effective antibiotic therapy in cases of documented intrauterine *Listeria monocytogenes* infection to allow such a pregnancy to proceed to term. The relationship of an abnormal cervico-vaginal bacterial flora to initiate labor has conceptual validity in theory, but has yet to be conclusively demonstrated.

A meta-analysis to evaluate the efficacy of antibiotic prophylaxis/therapy for preterm labor revealed a mixed outcome pattern with only small improvements in pregnancy

prolongation, estimated gestational weight and birthweight. The data is considered insufficient to show a beneficial effect on neonatal morbidity or mortality.

Key problems in evaluation of such data are the entry criteria for what constitutes preterm labor and, because of the rarity of morbidity and mortality, to have to rely on surrogate outcomes.

Overall, Thorp *et al.* concluded that the evidence supported the conclusion that antibiotic prophylaxis/ treatment resulted in small improvements in pregnancy parameters. Among the antibiotics used in these studies, none demonstrated superiority to the others.

The majority of the studies reviewed excluded gravida with preterm labor associated with rupture of the fetal membranes. Ascending infection occurs in the setting of ruptured fetal membranes and to a lesser degree in gravida with marked cervical dilation but intact membranes. A few papers exist in which eradication of occult or overt chorioamnionitis resulted in pregnancy prolongation.

ENDOCARDITIS PROPHYLAXIS

The current recommendation of antibiotic prophylaxis for women with known predisposing conditions in labor or undergoing an abortion has done a great deal in blunting the incidence of postpartum endocarditis (Tables 8.2 and 8.3). The potential for acute endocarditis exists and should be kept in mind when women with postpartum or post-aborted infectious complication

Table 8.2 Recommendations of the American Heart Association categories of patients for prophylaxis

Prosthetic heart valves
Rheumatic valvular disease
Bicuspid aortic valves
Ventricular septal defect
Mitral valvular disease (including mitral valve prolapse when insufficiency present)
Surgical shunts

exhibit an atypical clinical response to therapy or develop a murmur. When patients are sensitive to penicillin or its degradative product, alternate regimens must be used (Table 8.4).

An area of growing controversy is whether or not to administer prophylaxis to women with mitral valve prolapse. Mitral valve prolapse occurs in approximately 6–10% of the population. The risk of endocarditis is projected to be five- to eightfold greater than that of individuals without mitral prolapse. Of 52 cases of failure of endocarditis prophylaxis, one-third occurred in individuals with mitral valve prolapse as their underlying cardiac lesion. While the reputed risk of developing endocarditis is reputedly low, the American Heart Association recommends prophylaxis specifically for mitral valve prolapse with

insufficiency. Strasbert reported a case of postpartum endocarditis in a woman with mitral valve prolapse after vaginal delivery and specifically questioned the recommendations on the issue of mitral valve prolapse prophylaxis.

The American Heart Association recommends prophylaxis for vaginal hysterectomy but not for uncomplicated vaginal delivery, stating that endocarditis after uncomplicated vaginal delivery occurs rarely, if ever. Until definitive recommendations regarding prophylaxis for valvular heart disease and uncomplicated vaginal delivery have been finalized, decisions on prophylaxis should be made on an individualized risk-benefit analysis.

GBS PROPHYLACTIC ANTIBIOTICS

In 1996, the Centers for Disease Control, American College of Obstetricans and Gynecologists and the

Table 8.3 Antimicrobial prophylaxis of bacterial endocarditis

Procedure	***Prophylactic regimen(s)***
For dental procedures (including cleaning) and surgery or instrumentation of the upper respiratory tract	Aqueous crystalline penicillin G (Intramuscular: Adults, 1000000 units; Children, 30000 units/kg) MIXED WITH procaine penicillin G (Intramuscular: Adults and Children, 600000 units) 30 to 60 minutes before procedure, then penicillin V (Oral:Adults, 500 mg; children less than 27 kg, 250 mg) every six hours for eight doses. Remark: For patients with prosthetic heart valves or those taking continuous oral penicillin for rheumatic fever prophylaxis, the addition of streptomycin (Intramuscular:Adults, 1 g; children, 20 mg/kg) 30 to 60 minutes before procedure is recommended. OR Penicillin V (Oral:Adults, 2 g; children less than 27 kg, 1 g) 30 to 60 minutes before procedure, then (Oral:Adults, 500 mg; children less than 27 kg, 250 mg) every six hours for eight doses. Remark:This regimen is not recommended for patients with prosthetic heart valves or those taking continuous oral penicillin for rheumatic fever prophylaxis.
For genituourinary tract or surgery or instrumentation	Penicillin-Containing Regimen Aqueous crystalline penicillin G (Intramuscular or Intravenous: Adults, 2000000 units; children, 30000 units/kg) OR ampicillin (Intramuscular or Intravenous:Adults, 1 g; children, 50 mg/kg PLUS gentamicin (Intramuscular or Intravenous:Adults, 1.5 mg/kg; children, 2 mg/kg) OR streptomycin (Intravenous: Adults, 1 g; children, 20 mg/kg) 30 to 60 minutes before procedure,then repeat both drugs every eight hours (if gentamicin is used) or every 12 hours (if streptomycin is used) for two additional doses.

Table 8.4 Prophylaxis of endocarditis in patients allergic to penicillins/cephalosporins

Vancomycin	
Children:	10 mg/kg intravenously over 60 minutes BEFORE the procedure
Adults:	1 gram intravenously over 60 minutes BEFORE the procedure
PLUS	
Erythromycin 500 mg per oral every six hours for a total of 8 doses.	
OR	
Streptomycin or gentamicin. The latter are reserved for patients undergoing surgical or instrumentational procedures on the genitourinary or gastrointestinal tract.	

Academy of Pediatrics introduced two divergent approaches for the prevention of perinatal group B streptococcal disease (GBS). The first of these was predicated on prenatal maternal screening for GBS colonization at 35–37 weeks gestation and offering intrapartum chemoprophylaxis. This approach was subsequently modified to include gravida with GBS bacteriuria and women who had previously given birth to a GBS infected neonate. The second approach was contingent on the identification of one or more risk factors which included preterm deliveries, preterm or prolonged rupture of the fetal membranes, intrapartum fever, prior GBS neonatal disease, and GBS bacteriuria.

The original algorithms developed for the prevention of early-onset GBS disease in neonates are presented in Table 41.2. Both approaches were recommended as equally acceptable.

Both approaches have been successful in altering GBS neonatal and maternal morbidity and mortality. Neither has completely eliminated the occurrence of GBS neonatal disease. The principal shortcoming of a risk-based approach was the fact that 20% of GBS neonatal disease occurred in women without demonstrable risk factors. With the bacteriological screening approach for maternal GBS, the problems inherent in culturing on appropriate media, number of sites needed to exclude GBS, and the ultimate site/technique for obtaining the screening culture assured less than 85% GBS detection.

Schrag *et al.* did a multi-state retrospective cohort study involving 5144 births in which they compared the efficacy of the two officially recommended approaches. In the screened group 18% of all gravida with GBS did not present with an identifiable maternal risk-factor. These investigators found that the risk of early-onset GBS disease was significantly lower among infants of screened women than among the infants in the risk-based group by approximately 50%. They concluded that based on their data recommendations that endorsed both strategies as equivalent be reconsidered.

Prior to 1996, it had been demonstrated that the universal administration of penicillin to all neonates would profoundly alter, but not totally eliminate, the incidence of ensuing neonatal GBS. The switch from a pediatric-directed approach for GBS early-onset disease to an obstetrical-directed approach was justified argumentatively by the significant maternal morbidity caused by GBS at parturition. In terms of risk-benefit analysis, the justification is less clear. Both penicillin and ampicillin carry with their

administration the risk of anaphylaxis. To date, anaphylaxis has not been described in a newborn.

If society's mandated goal on zero cases of early-onset GBS is to be met, it may require a combined obstetrical approach based on culture surveillance and pediatric approach based on universal neonatal penicillin administration.

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Part II
Organisms

9
Congenital viral infections

Prior to the advent of certain virologic and immunologic techniques, congenital viral infection was defined as disease present at birth or developing before the shortest known incubation period for the virus in the immediate neonatal period. Although still a valid documentation of congenital infection, it results in the recognition of only a limited spectrum of disease and excludes those cases of congenital infection whose incubation period is one standard deviation removed.

Congenital infection does not require either overt clinical disease or the presence of histologic lesions. As has been pointed out by René Dubos, “the determinants of the disease are not the same as the determinants of infection”. In its most rigid form the definition of congenital infection is the exposure *in utero* of the developing embryo or fetus to the antigenic determinants of presumably infectious virus particles and the subsequent elaboration of specific IgM antibodies of fetal origin.

Antigenic stimulation of the fetus *in utero* may result in the quantity of IgM immunoglobulins detectable in cord or neonatal serum being elevated above the anticipated values. Approximately 25% of infants with congenital rubella syndrome have appreciable elevations of their IgM level. In general, there is a positive correlation between elevated serum IgM and the severity of the clinical involvement.

When maternal viral infection occurs in gestation at any time other than the immediate perinatal period, the demonstration of persisting antibodies beyond three months of age constitutes highly suggestive evidence of congenital viral infection. Complete documentation of congenital infection is contingent on the recovery of the virus at parturition from presumptive sites of recovery, e.g. placenta, products of conception, fetal or newborn organs, urine, or cerebrospinal fluid. When dealing with abortion material or very early embryos, virus isolation or the use of organism-specific DNA products are the principal means of specifically documenting congenital viral infection.

10
Cytomegaloviruses

Phylogenetically, the cytomegaloviruses (CMV) are among the oldest viruses known. Their differentiation parallels that of individual species so that it is not unusual to have relative or absolute species specificity. As a result of years of adaptive evolution, the bulk of human infection is predominantly a subclinical phenomenon.

Taxonomically, the CMV belong to the herpesvirus group, which includes herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus, and the Epstein-Barr (EB) virus. A CMV particle measures approximately 1800–2000 A in diameter and is made up of a single molecule of double-stranded DNA and sequential layers composed of an icosahedral protein coat and a lipid envelope. The site of viral DNA synthesis is within the host cell nucleus (Figure 10.1). Consequently, histologic evidence of virus replication can be observed in the form of an intranuclear inclusion body which is characterized by both cytoplasmic and nuclear gigantism. The mature 'owl-eye' lesion of the CMV is distinct from the intranuclear inclusion bodies of herpes simplex and varicella-zoster viruses. The magnitude of diametric increase of the cell is 2–3 times that observed with other members of the herpesvirus group. The intranuclear inclusion retains a circular to ovoid configuration, stains basophilic with hematoxylin and eosin, and is Feulgen-positive. The intranuclear inclusion body of the HSV is irregular in contour, stains eosinophilic with hematoxylin and eosin, and is negative in a Feulgen reaction.

Infection with the CMV results in the establishment of latent infection. Unlike the case with either the HSV-1, HSV-2 or the varicella-zoster virus, clinically overt manifestations of virus replication are seldom seen. Except in the immunologically compromised individual and in the developing human fetus, the CMV rarely exhibit virulence for humans.

Spread is by intimate contact with biologic fluids containing infectious material, specifically, tears, saliva, urine, endocervical mucus, colostrum, and transfused blood. The demonstration of CMV in semen makes venereal transmission of the infection a distinct possibility.

CLINICAL INFECTION

Infectious mononucleosis-like syndrome

Being so well adapted to the human host, the CMV rarely produce clinically overt disease. The principal clinical syndrome which may alert a physician to possible primary maternal CMV infection is that of an infectious mononucleosis-like syndrome. This pattern of disease is characterized by febrile illness with high, irregular fevers lasting as

long as three weeks. Clinically, the patient demonstrates lethargy, malaise, and hematologic alterations indistinguishable from those of infectious mononucleosis. The most important physical findings are the absence of the tonsillitis or pharyngitis and the cervical lymphadenopathy which are characteristic of infectious mononucleosis. These two negative findings strongly reinforce the possibility of CMV infection.

Clinically, both relative and absolute lymphocytosis are present, with abundant atypical lymphocytes (12–55%). Levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase may or may not be abnormally elevated at this time. Although biochemical evidence of hepatitis may exist, the hepatic tenderness associated with either infectious mononucleosis or hepatitis type A or B viruses is characteristically absent. In rare instances, evidence of myocarditis or a rubella-like rash may be present. Specific tests for hepatitis-associated antigen and for the presence of specific antibodies to *Toxoplasma gondii* and the

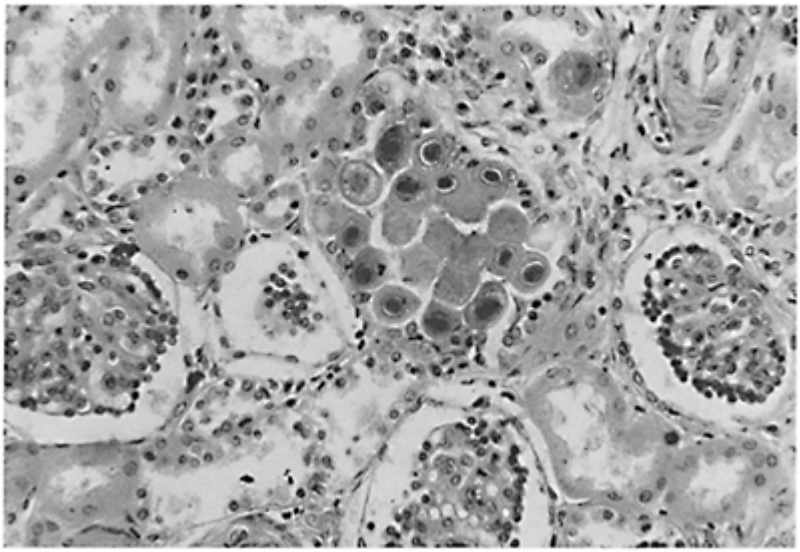

Figure 10.1 Classical intranuclear inclusion bodies in the renal tubular cells of an infant with congenital cytomegalovirus infection (H&E, ×420)

heterophil (Paul-Bunnell) reaction, if negative, aid in substantiating the diagnosis.

Significance of prior maternal infection

Both primary and recurrent maternal CMV infections are important in the pathogenesis of congenital infection. The overall prevalence for a given population is governed in part by

the prevalence of prior CMV infection. Women from middle to upper socioeconomic populations are less likely to have prior infection. Serosusceptibility in this population runs at 40–50% in contradistinction to 15% among those of low socioeconomic backgrounds. While women from middle-upper class socioeconomic backgrounds are more susceptible, they are also less likely to acquire primary infection during gestation. Primary maternal infection during gestation accounts for approximately 63% of cases of congenital infection in this group as opposed to 25% of congenital infections in the progeny of women from lower socioeconomic groups. The age distribution of the population similarly influences both prevalence and mode of fetal acquisition of infection. Women from low socioeconomic backgrounds acquire disease early in life. In this group congenital CMV is most often seen in the first born infant of teenage and young females. As a rule of thumb, the probability of vertical transmission associated with primary maternal infection is in the area of 35–40% whereas that associated with maternal CMV which antedates a pregnancy reaction is in the order of 1–3%.

While pregnancy *per se* does not alter the incidence of primary disease, viral shedding becomes a progressively more common phenomenon with time. On average, the prevalence of viral cervical and urinary tract shedding increases from 2.0% in the first trimester to 7.0% near term.

Age may also influence recurrent CMV shedding in the genital and urinary tracts of women. In low socioeconomic populations, the prevalence of CMV excretion in the genital tract is inversely related to age after puberty. The presence of CMV endocervical colonization is not a reliable marker for probable vertical transmission to the fetus. One cannot distinguish between viral excretion associated with primary disease and that of recurrent disease. Similarly, CMV viruria *per se* does not distinguish between primary infection and reactivation. Only when a high titer of urinary virus is present or demonstrable is there a markedly increased probability of delivery of a congenitally infected infant.

The overall incidence of congenital CMV among the progeny of seropositive women is approximately 1.8%. The overall incidence of congenital CMV infection in a general population is influenced by the composition of that population. It may range from 25 per thousand live births for single black women under the age of 20 to 1.6 per thousand live births for married white women over the age of 25. While maternal immunity cannot completely eliminate transplacental transmission, it appears to reduce the morbidity and deleterious consequences for the fetus/neonate. Prospective studies now indicate that recurrent maternal CMV is responsible for more cases of congenital infection than primary infection. This is particularly true for low socioeconomic populations.

CONGENITAL CYTOMEGALOVIRUS INFECTION

Congenital CMV infection has a prevalence ranging between 0.4% and 2.3% of all live births. Approximately 30000 neonates are born in the United States each year with congenital disease. Anywhere from 5 to 10% of these infants are clinically symptomatic at birth. Ninety percent of those who are symptomatic at birth develop major sequelae. Another 5–17% of neonates born with occult congenital infection will go on to develop varying degrees of complications during their preschool years. Anywhere from 2700 to

7600 babies are born each year who may develop developmental abnormalities caused by congenitally acquired infection.

Unlike congenital rubella, congenital infection with the CMV may occur despite the presence of strain specific humoral immunity. Being latent viruses of man, the CMV may undergo reactivation as well as prolonged shedding in biological fluid. Individuals with CMV infection tend to persistently or intermittently excrete virus in urine, breast milk, saliva, semen, cervical secretions, stools and tears. Viral shedding after primary infection normally persists for months or even years. With reactivation of latent infection the duration of shedding is significantly diminished. As a consequence of this type of reactivation of latent infection, there is a direct relationship between the incidence of congenital CMV and the rate of maternal seropositivity. Congenital infection resulting from recurrent CMV infection can and does occur in highly immune populations as well as in immunologically compromised individuals. There are at least three reports describing cases of congenital CMV infections in consecutive pregnancies.

Primary CMV infection occurs in 0.7–4% of pregnancies. With primary infection, fetal involvement occurs in 35–40% of the cases. Gestational age does not influence the rate of intrauterine infection following primary maternal infection. Stagno *et al.* prospectively followed 35 infants who were congenitally infected as a result of primary maternal infection. Only five neonates had clinical evidence of intrauterine infection at birth. The risk of primary maternal CMV infection leading to long-term sequelae is under 5%. The principal factor modulating this figure is when in gestation primary maternal infection occurred. Lipitz *et al.* evaluated 63 pregnant women with primary CMV disease for congenital transmission. Twenty-two (35%) of the pregnancies had virological or immunological evidence of vertical transmission. In nine (41%) of the 22 pregnancies with evidence of vertical transmission, abnormal ultrasono-graphic findings were recorded. The only pregnancy with prenatal ultrasonographic abnormalities that went to term resulted in an infant with neurologic sequelae. In the 37 pregnancies with no evidence of congenital infection which continued to term, only one of the ensuing pregnancies developed mild motor disability during a median of 23 months of follow-up.

Although based on limited observation, it appears that the CMV are capable of infecting the products of conception irrespective of their gestational age and that the clinical manifestations of congenital CMV infection

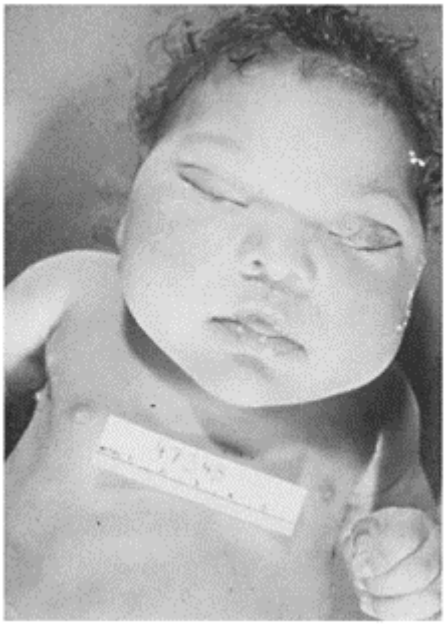

Figure 10.2 Marked microcephaly observed in fully developed congenital cytomegalovirus infection

appear to be primarily a reflection of the duration of infection *in utero*.

Analogous to maternal infection with rubella virus in the first trimester, two patterns of involvement of infection of the products of conception exist: one in which infection is limited solely to the placenta, and another in which both placental and panorgan fetal involvement occur.

First trimester infection

Early maternal disease does not invariably select for clinically overt disease, but when heightened neonatal morbidity occurs, it is most likely to do so in the progeny of women who acquired infection in the first trimester. The infants are usually premature or of a low birthweight for their term dates. The gross clinical presentation is often indistinguishable from the overt cases of congenital rubella, congenital toxoplasmosis, congenital herpes simplex virus infection, and congenital syphilis. The infant tends to be microcephalic (Figure 10.2). Roentgenograms of the head demonstrate extensive calcification of the lateral ventricles and portions of the olfactory tract. These have their anatomic correlation in extensive dystrophic calcification within necrotic subependymal areas of the lateral ventricles (Figure 10.3). Chorioretinitis is a frequent finding in those micro-cephalic infants with intracranial calcification. Hepatosplenomegaly due to extramedullary hematopoiesis, with or without superimposed hepatitis, is usually prominent. The infants

may have evidence of disseminated intravascular coagulopathy. Petechiae due to thrombocytopenia may be present at birth.

Infants with symptomatic congenital CMV have a very high likelihood of developing long-term sequelae. The follow-up studies of symptomatic infants by Boppana *et al.* have revealed a 41% rate of developmental delays, 53–61% rate of mental retardation, and a 100% need for special education.

In contrast, permanent sequelae which were permanent occurred in approximately 10% of asymptomatic congenital CMV infants. If infected infants were normal at one year of age, Ivarsson *et al.* reported that these children compared well in terms of neurological development and intellectual status to their peers.

Necropsy material has demonstrated panorgan viral involvement. The characteristic nuclear inclusion bodies have been identified in, or the virus has been isolated from, every organ system. Primarily involved is the epithelial cell, within which both cytoplasmic and nuclear enlargement are evident. In the mature lesions, nuclear inclusion bodies show peripheralization of the chromatin and central Feulgen-positive DNA mass, which electron microscopy reveals to be composed of complete and incomplete virions.

The CMV have been incriminated as a significant cause of fetal wastage. Griffiths and Baboonian have shown that fetal loss occurs in approximately 15% of gravida who contract CMV infection early in gestation as opposed to noninfected individuals (2.2%). Characteristic intranuclear inclusion bodies have been identified within alveolar macrophages of macerated small fetuses. The CMV have been isolated from aborted material. Studies on abortion material reveal an incidence of virus recovery ranging from 0.5% to 10%. These figures may be inflated. A certain percentage of this merely represents contamination of the products of

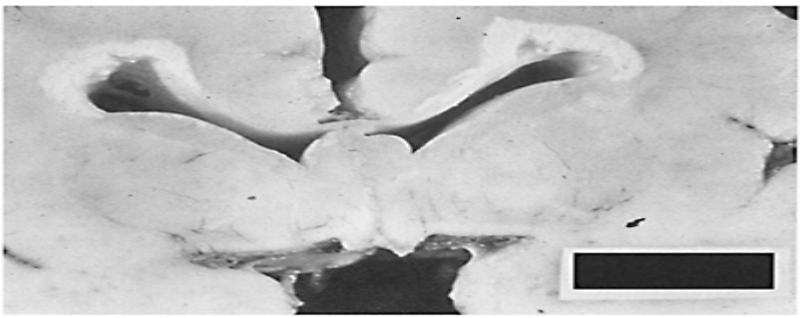

Figure 10.3 Extensive dystrophic calcification involving the lateral ventricles in an infant with congenital cytomegalovirus infection. (Reproduced with permission from Monif GRG. *Viral Infections of the Human Fetus.* New York, Macmillan, 1969)

conception as they pass by virus present within the endocervix and birth canal and does not reflect true congenital involvement.

Second trimester infection

When second trimester congenital infection results in clinically overt symptoms and postnatal morbidity, the clinical manifestations are much more protean than those observed following first trimester involvement. Microcephaly occurs but is not associated with a predominantly subependymal pattern of CNS dystrophic calcification.

Chorioretinitis is much less frequently observed. Some infants are born with hepatosplenomegaly (Figure 10.4) or hepatomegaly, with or without evidence of disseminated intravascular coagulopathy or jaundice. Other infants may have only elevated IgM levels as a consequence of congenital infection.

Third trimester infection

Third trimester involvement seems to be associated with a neonate who exhibits no early impairment of somatic growth or mental development. The infant tends to be normal by every parameter of gross measurement. Whereas specific IgM antibodies can be identified in cord serum, the IgM levels are only rarely elevated.

Late developmental sequelae

A primary question has been whether or not clinically inapparent disease might adversely affect the infant at a later date. What are the delayed morbid effects of occult neonatal infection? A longitudinal study of 16 infants with inapparent congenital CMV infection and elevated umbilical cord IgM levels revealed some degree of sensorineural hearing loss in nine of the 16. An auditory handicap was either proven or considered likely in four infants. Evidence of congenital CMV

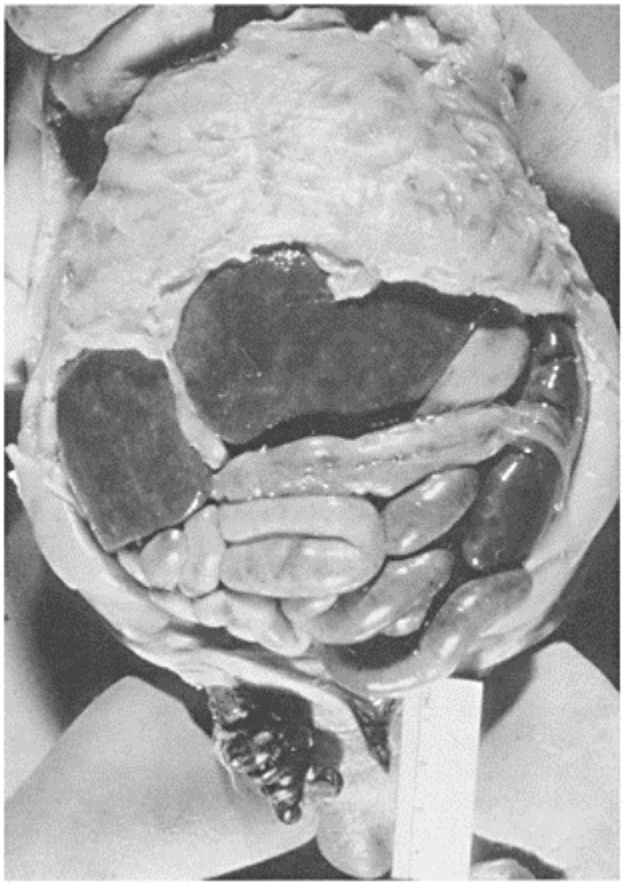

Figure 10.4 Hepatosplenomegaly, a finding characteristic of more severe chronic cases of intrauterine viral infection. (Reproduced with permission from Monif GRG. *Viral Infections of the Human Fetus.* New York, Macmillan, 1969)

infection can be detected in 12% of children with sensorineural hearing loss. This type of hearing loss is progressive.

A trend toward subnormal intelligence was observed in infected children. Hanshaw has postulated that clinically important mental and auditory impairment may occur in one out of every 1000 live births as a result of congenital CMV infection. Asymptomatic fetal CMV infection has been shown to produce long term damage in 10 to 15% of these infants. The long term damage which includes developmental problems, hearing loss,

mental retardation and motor deficiences, usually manifests within the first two years of life.

Postnatal dissemination

Gestational age has a significant influence on the rate of maternal CMV excretion. On average the prevalence of excretion increased from 2.6% in the first trimester to 7.6% near term. With parturition, breast milk becomes an additional vehicle for the transmission of virus from mother to progeny.

While there is a poor correlation between cervical and urinary CMV excretion during pregnancy and fetal involvement, there is a positive correlation between maternal viral shedding and postnatal acquisition of infection. According to the data of Stagno *et al.*, the two most efficient sources of transmission are: infected breast milk, which resulted in a 63% rate of postnatal infection, and the infected genital tract, particularly in late gestation. The age of the mother influences the frequency of viral excretion into the genital tract and breast milk. Younger seropositive women from lower socioeconomic groups who breast-feed are at the greatest risk for transmitting virus to their progeny.

The incubation period of CMV infection acquired during the perinatal period ranges between four and 12 weeks (average eight weeks). CMV infection acquired in the neonatal period occasionally results in clinical illness. The majority of infants with postnatally acquired CMV infection are asymptomatic. Postnatally acquired infection does not appear to adversely affect neurological or psychomotor functions.

DIAGNOSIS

Maternal infection

The serologic diagnosis of a primary CMV infection can be confirmed by the appearance of specific antibodies in convalescent sera (seroconversion). These antibodies, which can be detected by immunofluorescence, indirect hemagglutination and enzyme-linked immunosorbent assay appear within two weeks after primary infection. Antibodies measured by complement fixation and neutralization tests follow with one to two and four-week delays, respectively.

Serum-specific IgM antibodies can be demonstrated during the acute phase of primary CMV infection.

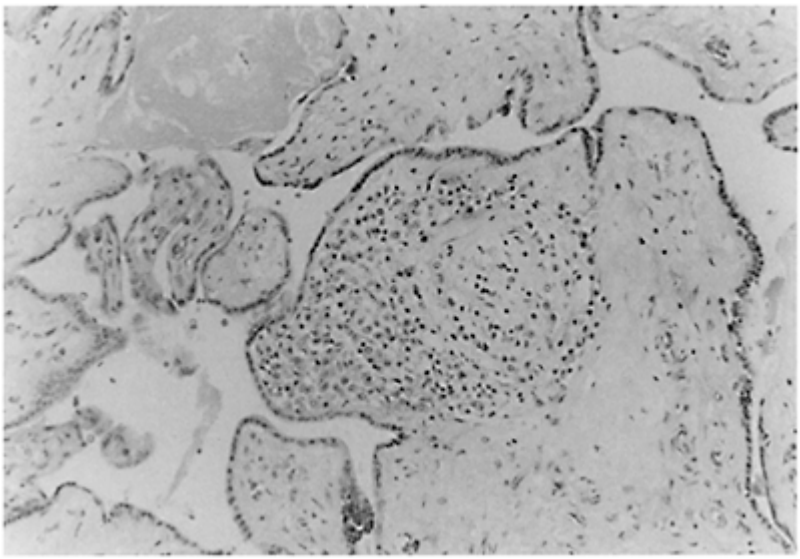

Figure 10.5 Cytomegalovirus placentitis: focal collection of plasma cells and lymphocytes within a chorionic villus. The presence of the characteristic intranuclear Inclusion bodies is rare. The persistence of Hofbauer cells and the edematous, relatively avascular villi with focal fibrosis should suggest the possibility of congenital cytomegalovirus infection. (Reproduced with permission from Monif GRG, Dische RM. *Am J Clin Pathol* 1972; 58:445. Copyright 1972, American Society of Clinical Pathologists)

Recent maternal infection can be inferred from a single serum specimen by the demonstration of IgM specific antibody. IgM antibodies appear early in the course of the disease and persist for 4 to 8 months depending upon which test is used. A rise in antibody titer or a single high titer (>1:108) correlates poorly with vertical transmission unless IgM specific antibody is present. Of all the tests available for this purpose, radioimmunoassay appears to be the most reliable because in normal hosts, including pregnant women, positive results occur only during the acute phase of primary infections and not with reactivations. With this test, specific IgM antibodies are detected in nearly

90% of women with a primary CMV infection and the antibody response persists for up to four months. False-positive IgM tests can occur. The clinician needs to take care that a reliable laboratory is performing the test.

Congenital infection

Placental pathology

Gross and microscopic inspection may provide inferential evidence of the possibility of congenital CMV infection. The placenta tends to be large, pale, and edematous. Intranuclear inclusion bodies are difficult to find. Their identification is often contingent upon a meticulous search. The villi and villous trunks frequently appear edematous. Focal collections of plasma cells intermixed with lymphocytes may be present (Figure 10.5). Characteristically, there is persistence of Hofbauer cells. Focal hemosiderin pigment is often identified free and in macrophages in areas of apparent endothelial damage and fibrosis. Only 25% of CMV placenta have the demonstrable histological criteria necessary for a definitive diagnosis. Immunohistochemistry can increase diagnostic sensitivity to 83%. Polymerase chain reaction (PCR) can detect 58% but if supplemented with Southern blot analysis after PCR, the combined sensitivity approaches 100%.

Cytology

Transformed renal cells shed into the neonate's urine can be diagnosed. Shedding of this type of cell is an intermittent phenomenon. The best urine sample for cytological analysis is an early morning urinary specimen with a high specific gravity.

Serological diagnosis

Maternally derived specific IgG antibody undergoes degradative elimination in the neonate; consequently, irrespective of whether or not intrauterine infection has occurred, the complement fixation titer falls to nondetectable levels. The reappearance of specific complement fixation activity 4–6 months after birth is consistent with either congenital or postnatally acquired infection.

Evidence of possible intrauterine infection may be inferred by the presence of elevated IgM levels in cord serum or blood samples obtained by funipuncture. Techniques for identifying IgM specific antibodies in cord blood are associated with a significant false-positive rate. Currently, the use of PCR testing on amniotic fluid for CMV is the best means of documenting *in utero* infection, short of viral recovery.

The immunoglobulins in the serum of the neonate, in the absence of congenital infection, reflect previous maternal experience with these agents and are predominantly of the IgG type. Since maternal IgM antibodies do not traverse the placenta and appear in the newborn serum, the finding of specific IgM or IgA antibodies is considered diagnostic of intrauterine infection. Diagnosis of congenital infection can also be made by demonstrating virus-specific antigens using PCR or ligase chain reaction (LCR) technology. Only 50–60% of CMV congenitally infected infants have IgM-specific antibodies at birth.

Virus isolation

Amniocentesis can provide material for virus isolation or PCR testing. Amniotic fluid analysis for CMV viral isolation and CMV PCR testing are the most sensitive ways of diagnosing congenital infection. Both Davis *et al.* and French *et al.* used amniocentesis to document congenital infection in women who had an infectious mononucleosis-like syndrome in the first three months of gestation. Stagno *et al.* have reported failure to recover CMV infection from amniotic fluid in three cases of primary maternal CMV infection (two of whom had isolation of virus from fetal and/or placental tissue).

Failure to isolate CMV from amniotic fluid does not necessarily rule out fetal infection. The recovery of virus strongly infers that vertical transmission has occurred. Virus isolation techniques are applicable for the isolation and identification of the CMV from tissue sources or amniotic fluid. The CMV can replicate successfully in fibroblastic tissue culture lines of human origin; the one most commonly utilized for isolation is WI-38. Specimens for viral culture need to be processed as rapidly as possible. Holding a specimen at 4ºC for 24 and 48 hours results in 14% and 32% false-negative rates. PCR and CMV shell vial assay to demonstrate the presence of virus specific antigens has partially displaced viral isolation techniques.

PRENATAL COUNSELING OF THE GRAVIDA WITH EVIDENCE OF PRIMARY CMV INFECTION

Prenatal counseling of a gravida with primary CMV infection is difficult. Negative amniocentesis fluid analyzed by both viral culture and PCR testing confer a reasonably high probability that the fetus is not infected at that time; however vertical transmission is possible at a later date in gestation.

In the series reported by Lipitz *et al.*, the use of a combination of prenatal tests resulted in an accurate diagnosis of all infected fetuses. Of the two procedures performed, amniocentesis provided the ability to identify all infected fetuses, using either amniotic culture and/or PCR analysis. The information yielded by funipuncture did not add to the ability of accurately diagnosing vertical transmission and, furthermore, had a sensitivity of only 77% in identifying infected fetuses. Regarding the two tests performed on amniotic fluid samples, the CMV culture identified all infected fetuses (among 13 tested), whereas the PCR missed one of 17 tested.

Although the ultrasound has limited sensitivity in the detection of fetal infection, pregnancies with evidence of vertical transmission and definite ultrasonographic findings indicating suspected fetal damage (such as hydrocephaly, microcephaly, ventricular abnormalities characteristic of ventriculitis, or brain or liver calcifications) are at significant risk of abnormal sequelae.

THERAPY

Currently in the United States, four medications have been approved by the FDA to treat CMV infections. Cidofovir and fomivirsen are approved for CMV retinitis. Ganciclovir and foscarnet are approved to treat visceral and disseminated CMV infections. The

documentation of maternal disease during gestation may be grounds for therapeutic abortion.

Ganciclovir, a homologue of acyclovir, has shown efficacy against CMV. It is the current drug of choice for life threatening or visceral CMV in immunocompromised individuals. Use of this drug is restricted to congenitally infected neonates with severe disease manifestations. Ganciclovir administration is associated with the induction of pan cellular bone marrow depression and requires skilled monitoring. Because of its teratogenicity and embrotoxicity in experimental animals, ganciclovir use is contraindicated in pregnancy. Attempts to use antiviral compounds in the treatment of severe congenital infection have met with mixed success.

There are no current recommendations for antiviral therapy in asymptomatic CMV neonates or infants.

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11
Enteroviruses

The enteroviruses are small, spherical, non-enveloped (naked) viruses that have icosahedral symmetry and a diameter of 27 to 30 nm. The virion is composed of a core of single-stranded RNA of about 7500 bases, with a molecular weight of 2.6×10^6. The viruses have a protein shell containing four polypeptide chains which are elements of 60 identical, four-segmented viral capsid protein subunits called protomers.

In terms of classification, the human enteroviruses are members of the Picornaviruses. They are divided into four major groups.

The enteroviruses are transmitted by both fecal to oral and oral to oral means of transmission. The ability to isolate enteroviruses in any age group is inversely proportional to age.

Enterovirus infections are common during pregnancy. Their prevalence in a given community is governed primarily by the:

(1) time of the year; and
(2) presence or absence of prior immunity to antigenically related enterovirus serotypes.

In northern latitudes, enterovirus infections tend to occur during the summer and fall. This seasonal periodicity is less pronounced in more tropical climates.

The majority of enterovirus infections result in asymptomatic or limited nonspecific febrile illness associated with primarily upper respiratory symptoms. Some patients will experience a brief but severe illness in which both fever and lower abdominal pain dominate. The abdominal pain tends to be midline and periumbilical in location and cramping in character. Experimental data suggesting that a higher incidence of clinical infections occurs with pregnancy

The sequelae of these clinical manifestations are potentially translatable into perinatal mortality. Although the bulk of maternal disease is subclinical or presents as nonspecific upper respiratory or gastrointestinal viral illness, maternal morbidity and mortality may develop as a consequence of meningoencephalitis, myocarditis or poliomyelitis.

MATERNAL ENTEROVIRUS INFECTION/DISEASE

The enteroviruses are quite prevalent in the environment. Their mode of transmission involves hand-to-mouth or more commonly vehicle (water-borne) dissemination. The gastrointestinal tract is the primary portal of infection. As a consequence, the prevalence of disease in the community tends to take on an epidemic pattern and can be significantly influenced by socioeconomic factors.

Most enteroviruses are relatively well adapted to man. Prior to development of the polio vaccines, for every case of paralytic poliomyelitis, there would be tens of thousands

of asymptomatic infections. The incubation period for infection shows significant variability, primarily due to inoculum dose effect and individual host factors.

In some cases, the pattern of maternal illness suggests the diagnosis of enterovirus infection.

While maternal infection is a common event, transplacental transmission of the virus is rare. However, when it does occur, and when that event is early in gestation, the consequences for the fetus are significant.

Transplacental transmission of the enteroviruses is primarily governed by magnitude and duration of the maternal viremia and the availability of complementary fetal viral receptor sites. The potential morbid consequences are primarily a function of gestational age and strain virulence. Viral membrane receptors change qualitatively and quantitively with gestational age.

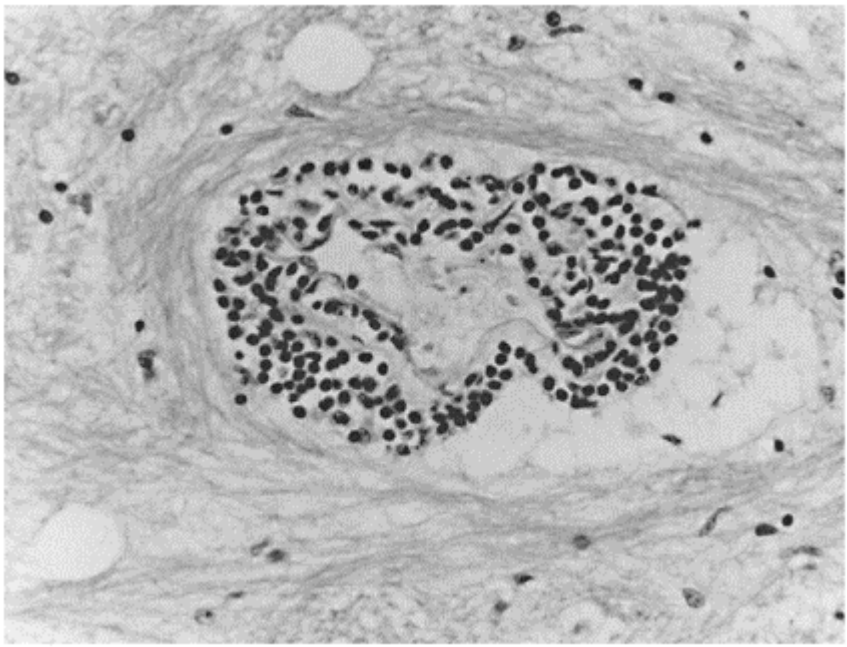

Figure 11.1 Photo of a neonatal brain infected with Coxsackie group B virus demonstrating perivascular “cuffing” with infliltration of the Virchow-Robin space by numerous mononuclear cells (H&E ×280). (Reproduced with permission from Monif GRG. *Viral Infection of the Human Fetus.* MacMillan, 1969)

MANAGEMENT OF ENTEROVIRUS INFECTION IN PREGNANCY

If acute maternal virus infection or disease is documented late in pregnancy, the fact that in rare instances fetal disease may occur needs to be presented, but in proper context. With the exception of the Coxsackie viruses, overt congenital disease is rare. The prognosis for the pregnancy outcome should be relatively optimistic. Management of maternal enterovirus infection is initially that of control of symptomatology. High maternal temperatures are to be avoided.

CONGENITAL AND NEONATAL INFECTION/DISEASE CAUSED BY THE COXSACKIE GROUP A AND B VIRUSES

The Coxsackie viruses currently account for 70% of all cases of serious neonatal disease. The dominant virulent Coxsackie B serotypes are B2, B3, B4, and B5.

In contrast to neonatal disease, overt congenital Coxsackie virus infection is a rare entity The majority of Coxsackie outbreaks in newborn intensive care units have their genesis in a premature or low birthweight infant who had contracted disease *in utero*.

Extensive disease *in utero* probably results in abortion, stillbirths or neonatal deaths. When fetal interstitial myocarditis is identified at necropsy, approximately half of these cases exhibit specific immunofluorescent staining for either the Coxsackie group A or B virus in the myocardium. The demonstration of significant fetal wastage caused by congenital Coxsackie viruses, coupled with the existence of occult congenital disease, indicates that a parameter other than clinical illness at birth is necessary to assess the true incidence of involvement. The long term consequences of occult congenital infection are not known.

Both congenital and neonatal infection with Coxsackie group viruses have been responsible for fulminating disease in newborns characterized by meningoencephalitis, myocarditis, and hepatitis (Figures 11.1 and 11.2).

The clinical manifestations are partially a function of the organ system which bears the brunt of the infection.

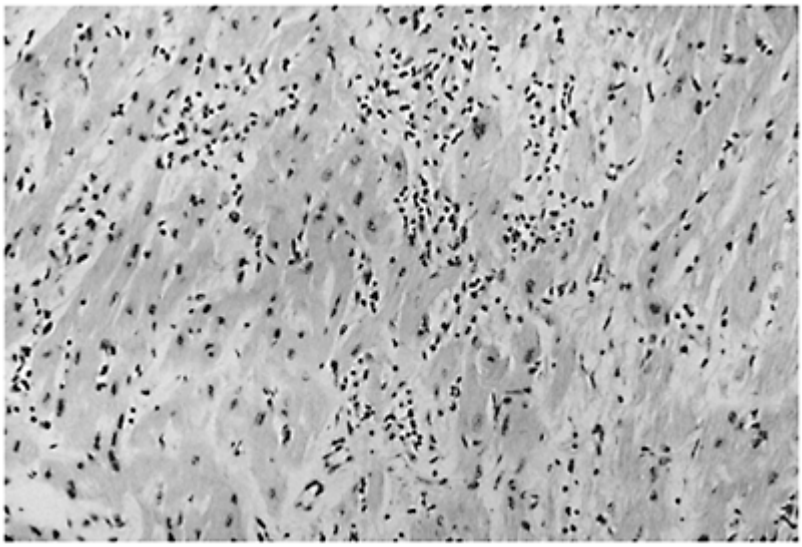

Figure 11.2 Interstitial myocarditis associated with myocardial necrosis in an infant with congenital Coxsackie group B infection (H&E ×280). (Reproduced with permission from Monif GRG. *Viral Infection of the Human Fetus.* MacMillan, 1969)

One organ system usually dominates the clinical picture. If sought, multi-organ involvement usually can be clinically demonstrated.

The onset of overt disease may be sudden or preceded by a period in which the neonate refuses feedings and exhibits mottling and cyanosis of the skin. Clinical evidence of myocarditis may include bradycardia, tachycardia out of proportion to the temperature, gallop rhythm, or a poor first heart sound. Electrocardio-graphic changes consist for the main part in alterations in the T wave, either flattening or inversion, depressed ST segments, low voltage QRS, disturbances of rhythm and conduction, or in some cases an injury pattern compatible with anomalous origin of the left coronary artery. In other cases, central nervous system involvement may overshadow the myocardial or hepatic manifestations of disease. These neonates are often irritable and present with bulging fontanels and cerebrospinal fluid pleocytosis. Death usually follows vasomotor collapse.

A number of studies have suggested that congenital infection resulting in selective cytopathic effect within the beta cell of the pancreas could lead to childhood-onset diabetes mellitus. Dahlquist *et al.* traced serum samples collected at time of birth from 55 mothers whose children later developed insulin-dependent diabetes mellitus (IDDM) and matched them pairwise to control subjects who gave birth at the same hospital during the same month. The sera were analyzed for IgM antibodies to Coxsackie B virus serotypes

2, 3 and 4 (CBV-2, 3 and 4) using a type-specific mu-antibody-capture radioimmunoassay. Despite a decreased power due to the close matching by time of birth they found a significantly higher frequency of CBV-3 IgM at delivery in mothers whose children later became diabetic compared to their matched control subjects.

Hyoty *et al.* initiated a prospective study designed to assess the role of Coxsackie B and other enterovirus infections in the induction and acceleration of this process. Three separate series were studied:

(1) an intrauterine exposure series comprising 96 pregnant mothers whose children subsequently manifested IDDM and 96 control mothers whose children remained nondiabetic;
(2) a cohort of 22 initially unaffected siblings of diabetic children who were followed until they developed clinical IDDM (mean observation time, 29 months) and 110 control siblings who remained nondiabetic;
(3) a case-control series comprising 90 children with newly diagnosed IDDM and 90 control subjects.

Enterovirus infections were identified on the basis of significant increases in serum IgG, IgM, or IgA class antibodies against a panel of enterovirus antigens (capture radioimmunoassay). Enterovirus antibodies were significantly elevated in pregnant mothers whose children subsequently manifested IDDM, particularly in cases in which IDDM appeared at a very young age, before the age of 3 years ($p<0.005$). Serological verified enterovirus infections were almost two times more frequent in siblings who developed clinical IDDM than in siblings who remained nondiabetic (mean, 1.0 vs. 0.6 infections/follow-up year; $p<0.001$). This difference was seen both close to the diagnosis of IDDM and several years before diagnosis.

Using the nationwide child-onset diabetes regiser in Sweden, Dahlquist *et al.* traced children who contracted diabetes before the age of 15 years and who were born at a specific hospital in Sweden where maternal sera from delivery had been stored during the years 1969–1989. Sera obtained at delivery from 57 mothers of diabetic children were compared with sera from control subjects who were delivered at the same hospital during the same time period. The sera were analyzed blindly using a group-specific enzyme-linked immunosorbent assay for specific IgM antibodies before and after urea wash as an avidity test. The mean absorbance values of enteroviral IgG antibodies against enteroviral antigens (echo-30, Coxsackie B5, and echo-9) were significantly higher among mothers whose children later developed diabetes ($p=0.002$, $p=0.02$, and $p=0.04$, respectively). When IgM activity and/or a significant decrease in avidity index, an indication of recent enterovirus infection, was used as a risk exposure, the odds ratio standardized for year of birth (95% confidence interval) was 3.19 (1.39–7.30).

These types of studies are part of a growing body of circumstantial evidence which may indicate that a fetal infection with the Coxsackie viruses similar to rubella virus may initiate autoimmunity or cause persistent infection that may lead to progressive beta-cell destruction.

Diagnosis

Congenital infection with the Coxsackie group B viruses is distinguished from its neonatal counterpart by the presence of the disease process at birth or its devel- opment in the first forty-eight hours of life. The diagnosis may be inferred prospectively or retrospectively on clinical or histological grounds because of characteristic target organ involvement. However, involvement of brain, heart, and liver is not a constant occurrence. Formes frustes of the disease are more likely to predominate. The diagnosis of subclinical disease is contingent upon the recovery of the virus from the products of conception and/or the neonate or the demonstration of specific IgM neutralizing antibody in the cord blood.

The enteroviral subgroups were originally differentiated from each other by their different effects in tissue cultures and in animals.

Even though many human tissue culture systems are capable of functioning as adequate indicator systems, virus recovery is best achieved in a biological indicator system, less than twenty-four-hour-old suckling mice. The identification of enteroviral types by neutralization in suckling mice or tissue cultures with antiserum pools is well-defined. Serologically, there are some minor cross-reactions between several enteroviral types, but there are no common group structural protein antigens of diagnostic importance.

Congenital and neonatal infections have been linked with many different enteroviruses, and representatives of all four major enterovirus groups have been associated with disease in the neonate. The serological diagnosis of enterovirus infection is impractical because there are no common group antigens making identification by each specific virus very time consuming and costly.

PCR testing of cerebrospinal fluid, blood, urine, and tissue specimens can be used in detecting the general viral group.

CONGENITAL ECHOVIRUS INFECTION

Transplacental dissemination of echoviruses occurs; infection in the fetus or neonatal is usually subclinical. To date, no recognized embryopathy or teratogenic sequelae have been identified. Johansson *et al.* report a case of intrauterine fetal death in the 29th week of gestation. Echovirus 11 was isolated from the umbilical cord of the fetus. The mother had only serological evidence of current echovirus 11 infection. Enterovirus PCR performed on paraffin-embedded specimens of various tissues (myocardium, lung, liver and placenta) from the fetus yielded positive results in all cases. These findings together with supporting serological and epidemiological finding—e.g. proven echovirus 11 infection 3 weeks before in the 18-month-old son of the woman—constituted evidence that echovirus 11 infection was responsible for the fetal death.

POLIOVIRUS

A high incidence of abortion does occur among gravidas who contract clinically overt poliomyelitis during the acute phase of their disease. Among the progeny born to mothers who contracted their disease early in gestation, there is a definite increase in incidence of prematurity and low birthweight neonates. Some of these infants exhibited impaired somatic development.

Poliomyelitis early in pregnancy may result in abortion or stillbirth. Whereas some cases are presumably related to the attending toxemia and hypermetabolic state, others may be the direct consequence of transplacental infection. Viral infection of the fetus later in gestation may result in premature deliveries or overt clinical disease at parturition.

CONGENITAL POLIOVIRUS INFECTION/DISEASE

Rare cases of overt poliomyelitis in newborn infants at parturition or within the first four days of life have been identified. The application of virologic techniques to the products of conception or the progeny of mothers whose gestation had been complicated by the development of poliomyelitis has demonstrated a significant occurrence of asymptomatic congenital infection. The clinical expression of poliovirus injection is contingent on their neurotropism rather than viscerotropism. Although potentially of etiologic significance with respect to the heightened incidence of miscarriage and abortion observed during maternal infection with the polioviruses during gestation, congenital infection with visceral involvement is probably insufficient in most instances for the production of clinically overt neonatal disease. It is only when the virus has the additional ability to traverse the ‘blood-brain barrier’ that *in utero* infection is manifested at birth or in the immediate neonatal period.

Overt congenital poliomyelitis, like its extrauterine counterpart, is a rare phenomenon with respect to the true incidence of infection. The meaning of visceral involvement in terms of somatic development and subsequent related morbidity has never been adequately evaluated because of lack of prospective virologic studies in the neonatal period and beyond.

The existence of both maternal and congenital subclinical disease invalidates many of the statistics concerning the probability of transplacental transfer. With the advent of the live vaccines, this entity has been basically reduced to a theoretical academic issue.

NEONATAL POLIOMYELITIS

Neonatal poliomyelitis is acquired due to either ascending infection associated with prolonged rupture of the fetal membrane or contact infection in association with parturition. Infants born to mothers whose disease manifested itself in the postpartum period exhibit a higher probability of ensuring neonatal neurological disease. This reflected the more prolonged and intimate exposure to the virus.

Congenital and neonatal poliomyelitis are clinically and pathologically indistinguishable. Characteristically, infants are lethargic and exhibit marked focal flaccidity. Cyanosis is a variable phenomenon predominantly related to the spinal cord involvement, affecting the muscles of respiration, and/or the presence of interstitial pneumonia.

At necropsy the dominant lesions involve the anterior horns of the spinal cord and the motor nuclei of the cranial nerves. The process is irregular in distribution and usually asymmetrical.

As in ‘adult’ poliomyelitis, interstitial myocarditis may occur. A focal interstitial pneumonitis may be present.

Diagnosis

The distinction between congenital and neonatal infection with the polioviruses is the presence of the disease process at birth or its development before the shortest documented incubation period for the polioviruses, five days. Both subclinical and overt congenital infection can be identified on the basis of virus isolation from placenta and neonate. Epithelial and fibroblastic tissue culture lines of human and primate origin afford adequate indicator systems for the recovery of the polioviruses. In dealing with necropsy material, primary monkey kidney tissue culture, in conjunction with agar overlay, constitutes the most sensitive indicator system for the isolation and tentative identification of any of the enteroviruses.

The diagnosis of congenital infection can be made on serologic grounds. This requires the demonstration of specific IgM antibody in cord serum or in the serum obtained in the immediate neonatal period.

Prophylaxis

One of the unresolved questions concerning therapy is whether a given patient with bulbar poliomyelitis should be allowed to go to term, and if so, the mode of delivery. Fragmentary reports suggest that certain patients benefit from the effect of terminating the pregnancy; however, it is stressed that the viability of the infant, progression of disease, and maternal vital capacity are the prime factors governing the mode of delivery.

The postpartum development of maternal poliomyelitis warrants immediate isolation of the infant. Once infection is initiated, gamma globulin is probably ineffective in aborting the disease or modifying the clinical severity of the disease.

The administration of live attenuated-poliovirus vaccines during pregnancy should be reserved for those situations where the clinical and epidemiological indications warrant their administration. Though mortality and morbidity caused by vaccine strains of the polioviruses are extremely rare, the vaccine strains of polioviruses can spread among susceptible family contacts and have produced clinical disease among vaccine recipients and family contacts.

LIVE VIRUS AND INACTIVATED VIRUS VACCINES

The risk of poliomyelitis is very small in the United States; however, epidemics could occur if the high immunity level of the general population is not maintained by vaccinating children routinely or if wild poliovirus is introduced into susceptible populations in communities with low immunization levels.

Two types of poliovirus vaccines are currently licensed in the United States: OPV (live virus) and eIPV (inactive). A primary vaccination series with either vaccine produces immunity to all three types of poliovirus in >95% of recipients. The primary series of OPV consists of three doses: two doses given 6–8 weeks apart and a third dose given at least 6 weeks and customarily 12 months after the second. The primary series for eIPV consists of three doses: two doses each given 4–8 weeks apart and a third dose given 6–12 months after the second. A primary vaccine series need not be given to adults living in the United States who have not had a primary series as children. However, for adults who have not had a primary series and who are at greater risk of exposure than the general population to wild polioviruses because of foreign travel or occupation, eIPV is preferred because the risk of OPV-associated paralysis is slightly higher among adults than among children. Poliovirus vaccine is not routinely recommended for persons older than high school age (≥18 years old).

Vaccine adverse reactions

Inactivated poliovirus vaccine

No serious side effects of currently available eIPV have been documented. Because eIPV contains trace amounts of streptomycin and neomycin, hypersensitivity reactions are possible among persons sensitive to these antibiotics. Persons with signs and symptoms of an anaphylactic reaction (e.g., hives, swelling of mouth and throat, difficulty breathing, hypotension, or shock) after receipt of streptomycin or neomycin should not receive eIPV. Persons with reactions that are not anaphylactic are not at increased risk and may be vaccinated.

Oral poliovirus vaccine

In rare instances, administration of OPV has been associated with paralysis among healthy recipients and their contacts. The risk of vaccine-associated paralytic poliomyelitis is extremely small for immunologically normal vaccinees (approximately one case per 1.4 million first doses distributed and one case per 41.5 million subsequent doses) and for their susceptible immunologically normal household contacts (approximately one case per 1.9 million first doses distributed and one case per 13.8 million subsequent doses). However, vaccinees should be informed of this risk.

Vaccine precautions and contraindications

Inactivated poliovirus vaccine

No convincing evidence of adverse effects of eIPV for the pregnant woman or developing fetus exists; regardless, theoretically vaccination of pregnant women should be avoided. However, if immediate protection against poliomyelitis is needed, OPV, not eIPV, is recommended.

Oral poliovirus vaccine

Unlike other live virus vaccines that are administered parenterally, OPV is administered orally. Immunoglobulin and other antibody-containing blood products do not appear to interfere with the immune response to OPV.

OPV should not be administered to persons who are or may be immunocompromised as a result of immune deficiency diseases, HIV infection, leukemia, lymphoma, or generalized malignancy or to persons who are or may be immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

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12
The hepatitis viruses

At least four distinct viruses causing human hepatitis have been distinguished to date on the basis of their biologic, physiochemical and antigenic characteristics (Table 12.1).

HEPATITIS A VIRUS (HAV)

Hepatitis A virus (HAV), formerly called infectious hepatitis (IH) virus or MS-I virus, most closely resembles the picornaviruses. The virus is approximately 27 nm in diameter and appears to have cubic symmetry. Degradative analysis has revealed three major polypeptides as well as the presence of a genome of linear single-stranded RNA. The polypeptides have molecular weights similar to three of the four polypeptides of enteroviruses. HAV is stable in the presence of ether at acid pH and is relatively resistant to heat. In 1969, Holmes and Deinhardt succeeded in transmitting HAV to marmoset monkeys. The subsequent detection of HA antigen (HAAg) in the serum and liver of infected marmoset monkeys, by Hilleman and associates, paved the way for the development of the current tests for hepatitis A antibody (anti-HAV).

The prime portal of infection in hepatitis A is the gastrointestinal tract. Disease follows an incubation period of 30–80 days. Hepatitis A antigen (HAAg) can be demonstrated in the stool for up to two weeks before the onset of illness. Shedding of antigen is maximal before onset of illness, but HAAg is still found in low amounts in about 50% of the serologically confirmed cases of hepatitis A during the first week of illness and in about 25% during the second week. This prolonged excretion of virus from the gastrointestinal tract is subclinical, and designates man as the prime reservoir of the virus. The disease has been reproduced in human volunteers following the oral ingestion of virus-containing material.

The virus resists heat inactivation at 56ºC as well as freezing for 1/2–1 hour. It can maintain its infectiousness for prolonged periods. Because of the high probability of encountering virus-containing material, susceptible subjects are probably infected at an early age. As might be anticipated, there is a seasonal nosologic distribution for HAV, with a low incidence in midsummer and a peak in late winter and early spring. The incidence of overt HAV infection is highest for individuals under 20 years of age. The peak incidence of disease in this age group can be interpreted as reflecting the prevalance of HAV and secondarily its contagiousness for susceptible contacts. Secondary cases are not uncommon. In these cases hand-to-mouth dissemination appears to be the mode of transmission. Nevertheless, the majority of cases of both clinical and subclinical forms of hepatitis A are the result of waterborne viral spread. Epidemics have been shown to occur under conditions of poor sanitation as water-borne epidemics or in association with the ingestion of raw oysters or hardshell clams bred in polluted water. The relative incidence

of icteric versus nonicteric cases of hepatitis A is not known. The ratio between the two may be analogous to that of the poliovirus, where poliomyelitis is like the tip of an iceberg in contrast to the bulk of subclinical infection.

HEPATITIS B VIRUS (HBV)

Hepatitis B virus (HBV) was previously designated serum hepatitis virus or MS-II virus. The virus is grouped with the Hepadnaviridae. The virus gives rise to the appearance of various types of antigenic particles in the serum of affected individuals. The structure representing the causative virus is a double-shelled particle about 42 nm in diameter. It contains an inner core

Table 12.1 Hepatitis nomenclature

	Abbreviation	*Term*	*Definition/Comments*
Hepatitis A	HAV	Hepatitis A virus	Etiologic agent of 'infectious' hepatitis; a picornavirus; single serotype
	Anti-HAV	Antibody to HAV	Detectable at onset of symptoms; lifetime persistence
	IgM anti-HAV	IgM class antibody to HAV	Indicates recent infection with hepatitis A; detectable for 4–6 months after infection
Hepatitis B	HBV	Hepatitis B virus	Etiologic agent of 'serum' hepatitis; also known as Dane particle
	HBsAg	Hepatitis B surface antigen	Surface antigen(s) of HBV detectable in large quantity in serum; several subtypes identified
	HBeAg	Hepatitis Be antigen	Soluble antigen; correlates with HBV replication, high titer of HBV in serum, and infectivity of serum
	HBcAg	Hepatitis B core antigen	No commercial test available
	Anti-HBs	Antibody to HBs Ag	Indicates past infection with and immunity to HBV, passive antibody from HBIG, or immune response from HB vaccine
	Anti-HBe	Antibody to HBeAg	Presence in serum of HBsAg carrier indicates lower titer of HBV
	Anti-HBc	Antibody to HBcAg	Indicates prior infection with HBV at some undefined time
	IgM anti-HBc	IgM class antibody to HBcAg	Indicates recent infection with HBV; detectable for 4–6 months after infection
Hepatitis C	PT-NANB	Parenterally transmitted	Diagnosis by exclusion; at least two candidate viruses, one of which has been proposed as hepatitis

			C virus; shares epidemiologic features with hepatitis B
	ET-NANB	Enterically transmitted	Diagnosis by exclusion; causes epidemics in Asia, Africa and Mexico; fecal-oral or water-borne
Delta hepatitis	HDV	Delta virus	Etiologic agent of delta hepatitis; can cause infection only in the presence of HBV
	HDAg	Delta antigen	Detectable in early acute delta infection
	Anti-HDV	Antibody to delta antigen	Indicates present or past infection with delta virus

Adapted from Monif GRG. Viral hepatitis. In David Charles (Ed). *Obstetrics and Perinatal Infections.* Mosby Year Book Inc, 1993

of distinct antigenicity (HBcAg) which shows cubic symmetry and contains a molecule of circular double-stranded DNA of $1.6\times10_6$ daltons. The core particle is surrounded by a shell, hepatitis B surface antigen (HBsAg), composed of carbohydrate, lipid, and protein. HBsAg carries a common determinant and a number of major subdeterminants (designated d, u, w, and r) which are coded by the viral genome. HBsAg may also occur in the form of 22 nm spherical particles and as filaments of similar diameter but of variable length. The 42 nm HBV particle contains a DNA-dependent DNA polymerase that uses the circular double-stranded DNA of the core as a primary template.

The ability to specifically distinguish type A hepatitis from type B has focused on the existence of a form of hepatitis which is not related to either A or B. This is the so-called non-A, non-B hepatitis or hepatitis C. It is not clear whether this entity is the consequence of a single virus or several distinct viruses. Preliminary data obtained by immune electron microscopy have suggested envelopeless particles with cubic symmetry, measuring 27 nm.

No cross-immunity between HAV and HBV has been demonstrated *in vitro* and *in vivo*. Individuals previously exposed to HAV are immune to rechallenge with HAV.

The prime portal of entry for HBV was thought to be the parenteral injection of blood or blood products derived from a healthy carrier of serum hepatitis, but this need not be the case. The ingestion of infectious material can induce either infection or disease in presumably susceptible individuals. HBsAg has been detected in many human biologic fluids, including saliva and semen, during acute infection. Person-to-person spread of hepatitis B has been documented among mentally retarded individuals in institutions and among intimate contacts, including sexual consorts of patients with hepatitis B or with persistent HBs antigenemia. Because HBV has a limited accessibility to a susceptible population, there is no peak incidence of disease, in contrast to the case with hepatitis A. Several valuable markers of hepatitis B were discovered during the decade of the 1970s. These include:

(1) hepatitis B surface antigen (HBsAg) and its respective antibody (anti-HBs, or HBsAb);
(2) hepatitis B core antigen (HBcAg) and its respective antibody (anti-HBc, or HBcAb); and

(3) hepatitis Be antigen (HBeAg) and its respective antibody (anti-HBe).

Both HBsAg and HBeAg are usually found in the serum of hepatitis B patients during late incubation and early clinical phases of the illness. Both antigens are detectable prior to the onset of jaundice or enzymatic abnormalities. HBsAg appears about 1–3 weeks after exposure and disappears after a period of 3 weeks to 3 months, while anti-HBs appears several weeks to a month following the clearing of HBsAg from the serum. Once present, anti-HBs will persist for years. The case fatality rate is approximately 1.4%.

HBcAg is not detectable in serum; however, anti-HBc is usually demonstrable at the time of onset of jaundice and abnormal enzyme chemistries. Anti-HBc, like anti-HBs, tends to persist once it is present.

HBeAg is demonstrable by solid-phase radio-immunoassay for a relatively short period of time and usually disappears before HBsAg has been cleared from the serum. The persistence of HBeAg tends to correlate with a prolonged course of illness and appears to have prognostic value late in the course of the disease.

Anti-HBc appears following the disappearance of HBeAg. Disease follows an incubation period of 41–108 days. The host may influence the clinical expression of the disease. Millman has noted that patients with Down's syndrome, leukemia, lepromatous leprosy, or chronic renal failure and those undergoing renal dialysis tend to develop a chronic anicteric form of hepatitis associated with the persistence of HBs antigen, in contrast to normal individuals, in whom the disease is clinically overt but of a shorter duration. In a small epidemic of hepatitis B among the patients and staff of a renal dialysis unit, infection occurred among nine patients and six staff members within one year. The disease among the staff members was characterized by acute overt clinical disease with elevated bilirubin levels and serum glutamic pyruvic transaminase (SGPT) levels over 1000 units. The SGPT elevations were less than 10 weeks in duration. The patients undergoing dialysis exhibited SGPT levels under 1000 units, but these elevations persisted for 20 weeks or more.

Chronic hepatitis B infection

The serum of a small percentage of individuals with hepatitis B will exhibit a persistence of HBs antigenemia. Two patterns are evident among the chronic HBsAg carriers. Chronic infection may be characterized by either:

(1) a prolonged period of abnormal serum transaminase activity and by persistence of HBsAg, HBeAg, and anti-HBc or
(2) persistence of HBsAg and anti-HBc associated with normal serum transaminase activity, the disappearance of HBeAg, and the subsequent appearance and persistence of anti-HBe.

Both forms of chronic hepatitis B pose unique problems for the offspring of mothers with HBs antigenemia. The attack rate of hepatitis B infection in infants born to mothers with the active type of chronic infection is very high—it usually exceeds 50%. In the case of mothers who are asymptomatic chronic carriers, the attack rate of hepatitis B infection in infants is low—usually less than 10%.

HEPATITIS C (NON-A, NON-B HEPATITIS)

Traditionally when hepatitis developed in pregnancy, the principal clinical problem was to distinguish hepatitis A from hepatitis B. With the initial development of sophisticated serological tests, it became clear that there was an entity known as non-A, non-B hepatitis (NANBH). With further advancement in our technology and the development of a test system for hepatitis C virus (HCV), the natural history of this disease entity has begun to unfold.

According to the National Health and Nutrition Examination Survey of 1988–94 and other population-based surveys, estimates of the incidence and prevalence of HCV infection have been made. Nearly 4 million Americans are infected with hepatitis C. The infection is more common in minority populations (3.2% of African-Americans and 2.1% of Mexican-Americans) than in non-Hispanic whites (1.5%). The incidence of hepatitis C infection appears to be declining since its peak in 1989. Currently, approximately 30000 acute new infections are estimated to occur each year, about 25 to 30% of which are diagnosed. Hepatitis C accounts for 20% of all cases of acute hepatitis. Currently, hepatitis C is responsible for an estimated 8000 to 10000 deaths annually, and without effective intervention that number is postulated to triple in the next 10 to 20 years. Hepatitis C is now the leading reason for liver transplantation in the United States.

Parenterally transmitted NANBH accounts for 20–40% of acute viral hepatitis in the United States. Although it has traditionally been considered a transfusion-associated disease, studies of community-acquired NANBH and data from the Centers for Disease Control (CDC) national surveillance system have shown that 23–42% of NANBH cases are associated with IV drug use. In addition, 8–11 % are attributed to blood transfusion and 4–8% to healthcare occupational exposure. However, for as many as 57%, no source of infection can be identified.

The HCV is an RNA virus of the Flaviviridae family. Individual isolates consist of closely related yet heterogeneous populations of viral genomes (quasiispecies). Probably as a consequence of this genetic diversity, HCV has the ability to escape the host's immune surveillance, leading to a high rate of chronic infection. Comparing the genomic nucleotide sequences from different HCV isolates enables classification of viruses into several genotypes and many more subtypes.

Based on genomic sequencing, there are at least six distinct genotypes. Some of these genotypes appear to be sufficiently divergent from each other to suggest the probability that they represent different serotypes, biologically due to significant differences in their critical antigens.

Hepatitis C virus is a virus composed of a single strand of RNA containing approximately 10000 nucleotides (Table 12.2). The virus is a spherical, lipid-enveloped virus with a mean diameter of 35–50 nm. Different strains of HCV demonstrate a remarkable degree of nucleotide sequence diversity.

Hepatitis C antigen is primarily a disease which is able to spread by transfusion or the use of drug paraphernalia. HCV antibodies are detected in approximately 0.6% of blood donors in the United States. Its overall prevalence world-wide is comparable. However, there are within these populations high-risk groups defined as multiply-transfused hemophiliacs and intravenous drug addicts, in whom the prevalence of HCV antibodies

may reach 60–70%. The distribution of HCV antibodies in different populations is listed in Table 12.3.

Primary infection

After initial exposure, HCV RNA can be detected in blood in 1 to 3 weeks. Viremia is maximum at the onset of either clinical or subclinical disease. Within an average of 50 days (range: 15 to 150 days), virtually all patients develop liver cell injury, as shown by elevation of serum alanine aminotransferase (ALT). The majority of patients are asymptomatic and anicteric. Only 25 to 35% develop malaise, weakness, or anorexia, and some become icteric. Clinically overt hepatitis in the course of primary disease is rare unless the Japanese serotype is

Table 12.2 Hepatitis C virus

RNA Virus—single strand
Configuration: Similar to Flavivirus which includes dengue yellow fever, Japanese encephalitis virus Spherical, lipid-enveloped viruses with a mean diameter of 35–50 nm Different strains of HCV demonstrate a remarkable degree of nucleotide sequence diversity Based on genomic sequencing, there are at least six distinct genotypes Some HCV genotypes appear to be sufficiently divergent from each other to suggest the probability that they represent different serotypes, biologically due to significant differences in critical antigens
Mode of transmission: Transfusion, intravenous drug user, occupation hazard;75% anicteric Extra-hepatic manifestations not recognized
Serological response: HCV antibodies appear 6–12 months after the onset of infection/disease

Table 12.3 Distribution of HCV antibodies by presumed mode of transmission

Parental transmission	2.1%
Blood transfusion	4.8%
Parental drug abusers	0.5%
Hemodialysis patients	1.8%
Non-parental transmission (sexual exposure)	7.1%

involved, in which case it may be as high as 20–30%. Fulminant liver failure following HCV infection has been reported but is a rare occurrence. Antibodies to HCV (anti-HCV) almost invariably become detectable during the course of illness. Anti-HCV can be detected in 50 to 70% of patients at the onset of symptoms and in approximately 90% of patients 3 months after onset of infection. HCV infection is self-limited in only 15% of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal.

There are no associated extra-hepatic manifestations with acute, as opposed to chronic, hepatitis C infection.

Chronic infection

About 85% of HCV-infected individuals fail to clear the virus by 6 months and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. Multiple episodes due to this virus grouping can occur. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About one-third of patients have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients.

Chronic hepatitis C is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection. A small proportion of patients with chronic hepatitis C, perhaps fewer than 20%, develop nonspecific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many patients with chronic hepatitis C at the time of development of advanced liver disease.

The rate of progression is highly variable. Long term studies suggest that most patients with progressive liver disease who develop cirrhosis have detectable ALT elevations; these can, however, be intermittent. The relationship is inconsistent between ALT levels and disease severity as judged histologically. Although patients with HCV infection and normal ALT levels have been referred to as ‘healthy’ HCV carriers, liver biopsies can show histological evidence of chronic hepatitis in many of these patients.

One of the major problems with chronic hepatitis, which progresses to cirrhosis, is that three quarters of these people will have had no overt clinical signs or symptoms of disease. Extra-hepatic manifestations of chronic hepatitis C do occur. Because of the immunological responses, some of these patients will develop cryoglobulinemia with circulating polyclonal IgG and IgM. Cryoglobulins may be detected in the serum of about one-third of patients with HCV, but the clinical features of essential mixed cryoglobulinemia develop in only about 1 to 2% of patients. These circulating immune complexes result in thyroid antibodies and, ultimately, Hashimoto’s thyroiditis, vasculitis, or membranous proliferative glomerulonephritis. Chronic hepatitis C may be a major underlying cause of porphyria cutanea tarda.

Cirrhosis of the liver

Chronic hepatitis C infection leads to cirrhosis in at least 20% of patients within two decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use. Alcohol appears to be a very important co-factor in the ultimate development of HCV-related cirrhosis.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a late complication of chronic HCV. The prevailing concept is that HCC ocurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately three or more decades. Most cases of HCV-related HCC occur in the presence of cirrhosis.

The risk that a person with chronic hepatitis C will develop HCC appears to be 1 to 5% after 20 years, with striking variations in rates in different geographic arease of the world. Once cirrhosis is established, the rate of development of HCC inceases to 1 to 4% per year. Among patients with cirrhosis due to hepatitis C, HCC develops more commonly in men than in women and in older than in younger patients.

DELTA VIRUS

Delta virus is a unique hepatotropic virus. It is composed of a single strand of RNA, of low molecular weight and an internal protein core. The Delta virus is 35–37 nm in size and is coded with the HBsAg. Its uniqueness comes from the fact that in itself it is incapable of attaching and hence infecting hepatocytes. Infection of the liver requires concomitant presence of the hepatitis B virus. The Delta virus must borrow hepatitis B surface proteins which permit attachment and subsequent infection of liver parenchymal cells. Without this critical step of attachment, there can be no infection.

The antibody response to Delta virus infection is of both IgM and IgG character. IgM anti-Delta antibody appears early during acute Delta virus infection and may persist for years owing to the presence of chronic infection. The IgG anti-Delta antibody occurs later in the course of acute infection. Chronic Delta hepatitis is usually associated with persisting high titer IgG antiDelta. Delta virus infection is a complicating factor in the course of acute hepatitis due to the HBV. It occurs either as a co-infection in the form of a more fulminant type of hepatitis or as a superimposed infection in a patient who is an antecedent chronic HBV carrier. Co-infection with hepatitis B/Delta virus usually causes an acute hepatitis. This infection is often clinically indistinguishable from that caused by the HBV alone. However, in selected instances disease may exhibit a biphasic course. The second set of enzyme elevations represent in this instance superimposed Delta virus infection. Co-infection appears to be associated with a higher rate of fulminant hepatitis; however, it does not increase the subsequent risk of becoming a chronic HBV carrier. The incubation period of hepatitis B/Delta co-infection ranges from 4 to 20 weeks. Clinical manifestations of superinfection of an HBV carrier range from asymptomatic liver enzyme elevations to fulminant hepatitis. Superinfection frequently results in the establishment of persistent Delta virus infection and constitutes the major reservoir of this virus. Chronic co-infection with HBV and Delta virus is associated with the development of chronic active hepatitis and cirrhosis. The diagnosis of Delta virus infection is made on the basis of detection of the Delta virus in serum during early infection, immunofluorescent staining of Delta antigen in liver or the appearance of Delta antibodies during or after infection. Testing for Delta virus is currently indicated in

fulminant HBV infection or, in the case of acute non-A hepatitis, infection occurring in a known HBV carrier.

Evidence of Delta virus infection has been found in up to 30–50% of people with fulminant hepatitis B. Co-infection has been associated with fulminant hepatitis, particularly in drug abusers. Delta infection is often related to occult blood contact suggesting sexual or inapparent percutaneous modes of dissemination similar to the HBV.

CLINICAL MANIFESTATIONS OF HEPATITIS VIRUS INFECTION

For most of the hepatitis viruses, overt disease tends to be more severe in adults than in children. During the prodromal phase of the disease, anorexia, lassitude, myalgia, arthralgia, headaches, and gastrointestinal symptoms are often manifested. In a significant number of cases of hepatitis B, a polyarthritis-like syndrome or arthralgias may occur several weeks before the onset of jaundice. The arthralgias tend to involve the smaller joints and are particularly evident at night. A small percentage of individuals, primarily women, may develop a maculopapular rash not unlike that of rubella or certain enterovirus exanthems. Fever, often accompanied by pseudochills, tends to occur shortly before the onset of clinically overt jaundice.

The earliest derangements of hepatic dysfunction are the appearance of bile in the urine. Darkening of the urine is detectable well in advance of clinical evidence of jaundice (this is usually indicative of a serum bilirubin level greater than 3 mg/100 ml). The urinary bilirubin test is useful in the detection of anicteric and pre-icteric hepatitis. Paralleling the rise in serum bilirubin is the increase in alkaline phosphatase. The SGOT and SGPT exhibit maximum titers just prior to the onset of jaundice. Early in the course of hepatitis A, the cephalin flocculation and thymol turbidity tests become positive. A SGOT/SGPT ratio of less than 1 is reputedly characteristic of viral hepatitis due to either type A or type B virus.

With the onset of jaundice the liver tends to enlarge and becomes tender. Histologically, it exhibits focal hepatocytic necrosis associated with a predominantly mononuclear cell infiltration both in areas of cell death and within the portal triad, as well as bile plugs and early bile duct proliferation. Individual hepatocytes may exhibit a rounding up and hyalinization similar to the Councilman body described in yellow fever. With electron microscopy it can be seen that the most uniform change is disruption of the rough endoplasmic reticulum (ER). This alteration of the rough ER seems to correlate best with decreased hepatocellular protein secretion. Hepatocellular death is indicated by the almost complete loss of glycogen and ER or by the occurrence of Councilman bodies, which are mummified whole cells. In these acidophilic bodies, the ER and even glycogen are preserved. A resultant increase in hepatic mass occurs because of the swelling of hepatocytes and the inflammatory infiltrate. They cause stretching of Glisson's capsule, which is responsible for the right upper quadrant tenderness and the positive 'hepatic punch' which is evocable at this time. Splenomegaly is not an uncommon finding and is said to be present in 25% of cases if carefully sought. If hyperbilirubinemia is prolonged, pruritus may be experienced.

The severity and persistence of hepatocellular destruction determines much of the subsequent clinical course. When hepatocellular necrosis is extensive, nausea, vomiting, and derangement of the higher cortical functions ultimately develop. This type of fulminating extensive hepatocellular destruction is more commonly due to HBV. It is to be noted that patients in coma may exhibit liver function tests indicative of a predominantly obstructive phenomenon. The SGOT and SGPT levels may be only moderately elevated, in contrast to the marked elevations of bilirubin and alkaline phosphatase; nevertheless, the SGPT tends to be more elevated than the SGOT. Coma is a reflection of a metabolic encephalopathy which in turn is a consequence of too little functional hepatocellular tissue.

As a rule, the peak SGOT and SGPT elevations occur within one or two days before or after the onset of jaundice. With massive necrosis, there is a collapse of the supporting reticulum for the destroyed hepatocytes. At this time the liver is no longer palpable, and death is imminent if aggressive supportive therapy is not instituted promptly.

The differential diagnosis of hepatocellular necrosis during pregnancy is limited: the hepatitis may be due to

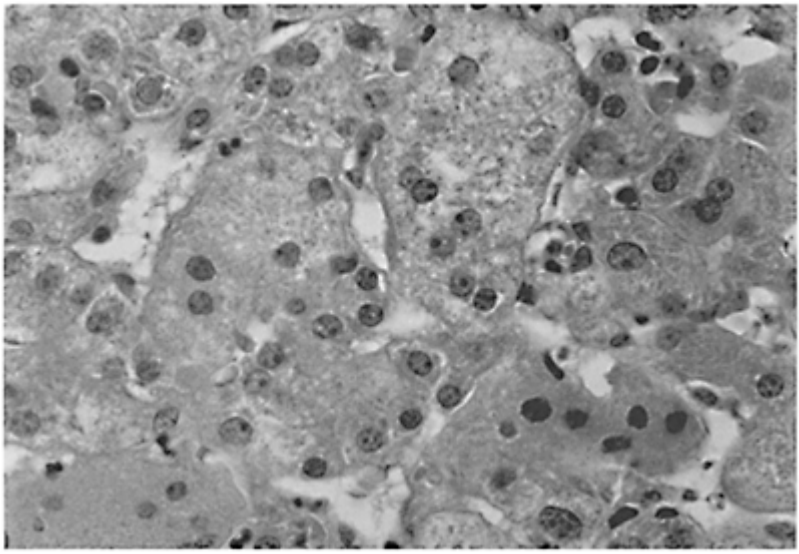

Figure 12.1 Giant-cell transformation characterized by ballooning of hepatocytes and dissolution of cell membranes in a case of neonatal hepatitis (H&E, ×480). (Reproduced with permission from Monif GRG. *Viral Infection of the Human Fetus.* New York: Macmillan, 1969)

HAV; HBV; non-A, non-B viruses; the cytomegaloviruses; Epstein-Barr (infectious mononucleosis) virus; idiopathic acute fatty metamorphosis of pregnancy; intravenous tetracycline therapy; alcoholic fatty metamorphosis; or chemical or drug hepatotoxicity. A careful history coupled with appropriate laboratory tests will provide the working diagnosis in most instances. For those cases in which a specific etiology cannot be inferred with a high degree of probability, a liver biopsy is indicated.

In general, the clinical course in adults lasts 3–4 weeks. Amelioration of symptoms with the return of appetite and loss of lassitude accompanies the return of normal hepatic function. A significant diuresis usually occurs at this time. Late sequelae, such as subacute hepatitis or cirrhosis, are rare following acute hepatitis. There is no predictable association between the severity of clinical manifestations of illness and the probability of these complications; however, it is worth noting that subacute hepatitis has a predilection for postmenopausal women over the age of 40.

CONGENITAL HEPATITIS

No question by an expectant mother is more poignant to an obstetrician than "Will it affect my baby?" With respect to the hepatitides, the answer has been obscured by the previous inability to segregate cases of type B and C from type A hepatitis.

In a number of retrospective cases, neonatal hepatitis was found to have developed in children born to mothers whose pregnancy had been complicated by hepatitis. These cases tended to lend weight to the possibility that a form of viral hepatitis in the mother could be transmitted *in utero* to her progeny. Additional data along these lines were derived from infants dying of neonatal hepatitis in the immediate postpartum period. At autopsy, they were found to have lesions ranging from diffuse hepatic cell necrosis to advanced cirrhosis (Figure 12.1). The maturity of the latter lesion and the short interim between birth and demise made it certain that the disease had developed *in utero*. A tendency for the lesions to be more pronounced in the left lobe of the liver reinforced the concept of hematogenous maternofetal dissemination. Because affected newborn infants exhibited the late sequelae of viral hepatitis, namely posthepatic cirrhosis, it must be presumed that other cases had undergone complete remission of infection *in utero*.

The first body of data consistent with the hypothesis of transplacental viral infection was the work of Stokes *et al.* In 1951 Stokes and co-workers were able to reproduce clinical and laboratory evidence of hepatitis in human volunteers, with serum from a newborn baby with neonatal hepatitis and from its mother, who had had hepatitis during pregnancy. The failure to reproduce these findings obscured the issue until the recognition of HBsAg.

HAV vertical transmission

The ability of type A hepatitis to infect the fetus *in utero* has ony recently been documented. Leiking *et al.* reported a case of maternal hepatitis at 20 weeks gestation. At 27 weeks, ultrasound revealed polyhydramnios and fetal ascites. Through maternal testing, detailed fetal ultrasound, echocardiography, and funipuncture, the diagnosis was made by demonstrating abnormal liver tests, nonspecific findings of recent viral

infection, and hepatitis A virus IgM antibodies at the time of funipuncture. Maternal history and serologic testing also confirmed the diagnosis of hepatitis A in the mother 4 weeks before the appearance of fetal ascites.

HBV vertical transmission

HBsAg can cross the placenta and has been demonstrated in cord serum. In a prospective study of maternofetal transmission of HBV in 125 healthy mothers who were carriers of HBsAg, Lee *et al.* showed that the most important determinant in such transmission was the presence of HBeAg in the mother. HBsAg was detectable by solid-phase radioimmunoassay in 33% of the amniotic fluid samples, 50% of cord blood samples, 71% of breast milk samples, and 95.3% of samples of gastric contents from newborns. The absence of a tight correlation between HBsAg in the amniotic fluid and cord blood and the subsequent development of antigenemia in the babies suggested that intrauterine infection is not a primary mode of maternofetal transmission. Intrauterine infection accounted for those babies who had HBsAg-positive cord blood and who had HBs antigenemia from one month after delivery onward. However, these babies constituted only a small percentage of the series. Shen *et al.* were conclusively able to demonstrate the presence of HBV DNA in the serum of 13 neonates and in leukocytes of two neonates born to 16 HBeAg-positive gravida.

Unlike most other viral infections capable of transplacental transmission and infection, congenital type B hepatitis in one child may not confer immunity to subsequent offspring. Multiple instances of disease in successive pregnancies or alternate pregnancies have been documented. Typical is a case of Gruber's in which a gravida developed anicteric hepatitis, presumably caused by HBV, in the sixth month of pregnancy. She gave birth to a child who died shortly after birth with giant cell hepatitis (Figure 12.1). A year later another child died 48 hours after birth; at necropsy the infant exhibited multinucleated giant cells and periportal fibrosis. A biopsy of the mother's liver at this time showed changes consistent with chronic hepatitis.

One point worthy of comment is that transplacental transmission can be a two-way phenomenon. Maternal and neonatal hepatitis have been observed following intrauterine transfusion, but it is probable that the mechanism by which this occurs is markedly different from that of congenital infection.

HCV vertical transmission

In one series, a vertical transmission has been documented in 10 of 31 babies born to women positive for serum HCV RNA. The statistics obtained by Ohto *et al.* are very similar to those previously published by Thaler *et al.* The Ohto study presented evidence that the strongest correlation for risk of transmission was the titer of serum HCV in the mother. In these studies it is not clear to what extent one is dealing with congenital transmission and to what extent one is dealing with transmission owing to breast feeding.

NEONATAL HEPATITIS

Whereas congenital hepatitis is a relatively rare phenomenon, unfortunately neonatal hepatitis is not. Mothers with transient or persistent antigenemia at term can infect their offspring via body fluids. In the United States, an estimated 16000 births occur to HBsAg-positive women each year. Approximately 4300 of these women are HBeAg positive. These pregnancies result in 3500 neonates becoming chronic HBV carriers. Vertical transmission of HBsAg from mother to fetus may occur transplacentally or during the birth process. If the mother has acute disease in the immediate periparturitional period or exhibits HBe antigenemia, the probability of subsequent neonatal antigenemia at some time during the first year of life is of the order of 70–90%. Once infected, the infant tends to remain HBsAg-positive indefinitely, and the persistent HBs antigenemia is more likely to be associated with evidence of chronic hepatitis than if it were to occur in an adult. Up to 85–90% of infected infants will become chronic HBV carriers. It has been estimated that more than 25% of these carriers will die from primary hepatocellular carcinoma or cirrhosis of the liver. In Schweitzer's series of 20 infants whose mothers had hepatitis and who became HBs-positive, two developed acute mild hepatitis at 3 months of age, promptly recovered, lost their antigenemia, and developed significant antibody titers at six months. The remaining 18, who did not develop overt hepatitis, have now been monitored up to five years of age and all have remained persistently HBsAg-positive. Seven of these children have been monitored for at least four years. Clinically, the children have had variable transaminase elevations. Liver biopsies, performed on 10 of the 18 children between 3 and 27 months of age, have demonstrated the presence of a chronic viral hepatitis.

MANAGEMENT OF HEPATITIS IN PREGNANCY

Maternal considerations

Clinically overt maternal disease

It is commonly stated that during pregnancy, particularly during the second and third trimesters, the liver may be more susceptible to noxious stimuli than at other periods. Although this point is still moot, those workers who perform autopsies on pregnant women are impressed by the frequency with which fulminating hepatic disease is the cause of maternal mortality. This observation is the rationale for clinical management. Any pregnant woman with a rapidly rising SGOT and SGPT should be hospitalized and observed until such time as it can be demonstrated that the transaminase values have passed their maximum and are clearly falling toward physiologic levels.

There is no evidence that prolonged bed rest or a high-protein diet alters the course of the more common form of the disease. A policy of gradual ambulation and a diet on demand suffices in the majority of cases. For hepatitis, appropriate isolation procedures should be instituted during hospitalization.

The determination of the type of hepatitis may predicate whether or not hepatitis immune serum globulin should be administered to household contacts.

HBV asymptomatic infection

The CDC estimates that there are approximately 0.7 to 1.0 million chronic carriers of HBV in the USA and that this pool of carriers grows by 2–3% (8000 to 16000 individuals) annually. Chronic carriers represent the largest human reservoir of HBV. Increasingly more and more hospitals are instituting a prospective screening of all admissions for the presence of HBsAg. The identification of a pregnant woman about to deliver presents two problems: the possibility that she will function:

(1) as an effective vehicle for the dissemination of hepatitis B within the immediate medical environment; and
(2) as a potential horizontal and/or vertical vector for her progeny.

HBV nosocomial impact

Nosocomial transmission of HBV to staff and patients can be minimized by appropriate practices and environmental measures. All patients who are known at the time of admission to be HBsAg-positive should be placed on blood and discharge precautions. A mother may be HBsAg-positive, either because she has acute hepatitis B during pregnancy, or because she is a chronic carrier of the virus. The chronic carrier state is defined as HBs positivity at two points in time at least six months apart. The potential perinatal or nosocomial transmission is more dependent upon the presence or absence of HBeAg than on whether the patient has acute or chronic hepatitis. HBeAg-positive individuals are also potential vectors for individuals in their immediate hospital environment. Susceptible medical personnel who receive a needle-stick puncture from an HBe antigen-positive gravida have a 20% chance of developing infection. In contrast, HBsAg-positive mothers who are HBe antigen-negative seldom infect the neonates and these infants usually do not develop the chronic carrier state. Needle-stick injuries from HBe antigen-negative patients are much less likely to infect susceptible medical personnel. Nevertheless, the guidelines which have been developed by the CDC are recommended for all HBsAg-positive births regardless of the maternal HBe antigen status.

HCV antibody positive gravida

Management of an individual with anti-HCV antibodies requires:

(1) Challenging the validity of the initial observation. Repeat the test using a second generation enzymelinked immunosorbent assay (ELISA) test. If again positive, use a RNA assay.
(2) Monitor maternal serum ALT. Patients with serological evidence of HCV infection who demonstrate elevated HCV levels of their serum aminotransferase over six to twelve months should be deemed as having HCV infection and biopsied at some future date unrelated to pregnancy.

If chronic hepatitis activity is present for a prolonged period of time, the patient should be evaluated for possible treatment with recombinant interferon alpha. Pregnant patients should be counseled not to breast feed their infants. When possible general anesthesia should be avoided in gravida with anti-HCV antibodies and abnormal liver function tests.

PRENATAL SCREENING FOR HEPATITIS B AND C VIRUS

In 1984, the Immunization Practices Advisory Committee (ACIP) recommended that pregnant women in certain groups at high-risk for HBV infection be screened for HBsAg during a prenatal visit and, if found to be HBsAg-positive, that their newborns receive hepatitis B immune globulin (HBIG) and HB vaccine at birth (Table 12.4).

Unfortunately, screening limited to high-risk individuals identified less than 50% of chronic HBV carriers. Routine screening of all pregnant women is the only strategy which will significantly impact on perinatal transmission.

HbsAg testing should be done early in pregnancy when the other routine prenatal testing is done. The HBsAg test is widely available and has been added to the routine prenatal 'panel' of tests without requiring additional patient visits. The advantages of making HBsAg testing routine during early pregnancy include:

(1) the ability to identify HBV carrier mothers that is not dependent on the healthcare provider's identifying high-risk women or ordering HBsAg as a special test;
(2) the availability of test results before delivery so that infants can receive HBIG and HB vaccine without delay after birth; and
(3) appropriate counseling of families before delivery.

Because more than 90% of women found to be HBsAg-positive on routine screening will be HBV carriers, routine follow-up testing later in pregnancy is not necessary for the purpose of screening. In special situations, such as when the mother is thought to have acute hepatitis, when there has been a history of exposure to hepatitis, or when particularly high-risk behavior such as parenteral drug abuse has occurred during the pregnancy an additional HBsAg test can be ordered during the third trimester. Few women in populations at low-risk for HBV infection will have a change in HBsAg status during subsequent pregnancies. However, because of the expected benefits of making HBsAg testing a

Table 12.4 Recommended schedule of hepatitis B immunoprophylaxis to prevent perinatal transmission of hepatitis B virus infection

Infant born to mother known to be HBsAg* positive

Vaccine dose:**	**Age of Infant:**
First	Birth (within 12 hours)
HBIG[1]	Birth (within 12 hours)
Second	1 month

Third	6 months[2]
Infant born to mother not screened for HBsAg	
Vaccine dose:* **	**Age of Infant:**
First	Birth (within 12 hours)
HBIG1	If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second	1–2 months[3]
Third	6 months[2]

*HBsAg=Hepatitis B surface antigen
**Use appropriate dose
[1]Hepatitis B immune globin (HBIG)-0.5 ml administered intramuscularly at a site different from that used for vaccine
[2]If four-dose schedule (Engerix-B) is used,the third dose is administered at 2 months of age and the fourth dose at 12–18 months.
*** First dose=dose for infant of HBsAg-positive mother. If mother is found to be HBsAg positive, continue that dose; if mother is found to be HBsAg negative, use an appropriate dose for that situation.
[3]Infants of women who are HBsAg negative can be vaccinated at 2 months of age. (From CDC. MMWR 1991;40:1)

routine part of each prenatal panel, testing should be done during each pregnancy.

Women who present for delivery without prenatal care or without medical records documenting the results of HBsAg screening should have the HBsAg test done as soon as possible after admission.

The commercially-available HBsAg tests have an extremely high sensitivity and specificity if positive tests are repeated and confirmed by neutralization as recommended by the manufacturers of the reagent kits. Testing for other markers of HBV infection, such as HBeAg, is not necessary for maternal screening. Mothers who are positive for both HBsAg and HBeAg have the highest likelihood of transmitting HBV to their newborns. However, infants of mothers who are HBsAg-positive but HBeAg-negative may become infected and develop severe, even fatal, fulminant hepatitis B during infancy. For this reason, HBIG and HB vaccine treatment of all babies born to HBsAg-positive women is recommended. HBsAg-positive mothers identified during screening may have HBVrelated acute or chronic liver disease and should be evaluated by a physician. Identification of women who are HBV carriers through prenatal screening presents an opportunity to vaccinate susceptible household members and sexual partners of HBV carriers.

While HCV is not an official part of prenatal screening, it is only a question of time before it becomes one of the cornerstones of prenatal preventive care.

PERINATAL INFECTION

Most perinatal infection seems to occur at the time of delivery, not transplacentally or at the time of conception. Although maternal HBsAg has often been found in cord blood samples, its presence has not correlated closely with neonatal infection. Either external contamination of samples or maternal blood entering the placenta after fetoplacental circulation has ceased may account for this poor correlation.

The probability of developing the carrier state in infected neonates can be greatly reduced by using HBIG, provided it is used soon enough. A large clinical trial of HBIG, reported from Taiwan, showed that administering HBIG to infants within seven days of birth was unsuccessful, but using HBIG within 48 hours of birth (usually in the delivery room) proved highly successful in preventing the development of the carrier state in infants of mothers who were both HBsAg and HBeAg positive. Delay in administration of HBIG to infants of carrier mothers will decrease the efficacy of therapy. In the studies that demonstrated the highest efficacy (85–95%) of combined HBIG and HB vaccine prophylaxis, HBIG was administered within 2 to 12 hours after birth. In one study in which only HBIG was used for prophylaxis, no efficacy was found if HBIG was given more than seven days after birth, and a significant decrease in efficacy was observed if it was given more than 48 hours after birth. If the prenatal population can be prospectively screened, HBIG administration can be done in the delivery room. Infants born to these women should receive HBIG. The initial dose is 0.5 ml intramuscularly. in the delivery room, if possible, and certainly within 48 hours of birth. The injection site should be thoroughly cleaned before HBIG administration. This dose is repeated at three months and six months of age. The infant is born covered with maternal blood and other secretions containing the HBV, and these enter the eyes, mucous membranes, gastrointestinal (GI) tract, and sometimes the circulatory system. Cesarean section delivery does not prevent HBV infection. These infectious secretions constitute a risk not only to the neonate but also to those attending the delivery. ‘Blood precautions’ should be taken to protect staff and prevent environmental contamination that could lead to infection of others. Care should be taken with maternal blood and secretions before, during, and after delivery Attendants at delivery should wear gloves, face mask and glasses to keep infective material from splashing onto eyes or mucous membranes, and should be careful to avoid punctures from sharp instruments. The delivery room and instruments should be carefully cleaned and sterilized. Dressings soiled with lochia or wound exudates should be carefully handled. Sitz baths should be thoroughly cleaned and then wiped with a suitable high-level disinfectant. A 1/2 cup per gallon solution of 5.25% sodium hypochlorite is recommended. Infants whose mothers are chronic carriers will be continuously exposed to HBV throughout their childhood; therefore, these infants should receive HB vaccine. The optimum timing of vaccination in conjunction with HBIG administration has not been established. Pending the development of such data, it is recommended that vaccination be given at three months of age or shortly thereafter. The presence of passively acquired antibody from the mother, or that which results in HBIG administration does not appear to affect active immunization. Vaccination of individuals who possess antibodies against HBV from a previous infection or by passive acquisition will not cause an adverse effect. Such individuals will have a post-vaccination increase in their anti-HBs levels.

Even if the neonate is infected at birth, active viral replication will not occur for several weeks. After thoroughly washing off external contamination, the infant need not be separated from his mother or placed in special isolation. Washing and rinsing should be thorough and done carefully by a gloved attendant using soap or detergent and water. Vitamin K injections can wait until after the bath.

CDC RECOMMENDATIONS FOR BREAST FEEDING FOR HBsAG POSITIVE WOMEN

The question of breast-feeding usually arises in discussions of perinatal transmission. Although HBsAg has been detected in some samples of breast milk, some investigators required special concentration techniques to do so. Significant exposure to HBV via breast milk appears to be unlikely, especially after the relatively massive exposure occurring during the birth process. Studies from Taiwan have shown that breastfed infants of carrier mothers are no more likely to be infected at one year than are infants for whom breast-feeding was withheld. Cracked nipples, abscesses, or other breast lesions, however, could mix breast milk with highly infectious serous exudates, and feeding should be temporarily suspended from that breast until the lesion has healed.

The CDC has not formulated recommendations for breast feeding for HCV-antibody positive gravida. A critically important question is “Should mothers who are infected with HCV breast feed their babies?” The implication that breast-feeding may be a factor is suggested in the Ohto data. The duration of nursing for infected infants was 6.6±3.6 months as opposed to 2.0±2.9 months for uninfected infants whose mothers had HCV titers ≥10:6/ml

DIAGNOSIS

Hepatitis A

A plethora of methods, including immune electron microscopy, radioimmunoassay (RIA), enzyme immunoassay, immunoadherence, and complement fixation, have been developed for demonstrating either hepatitis A antigen (HAAg) or its antibody (anti-HAV). The diagnosis of acute hepatitis A can be established by demonstrating the presence of HAAg in the stool. Because chronic excretion of the virus has never been observed, demonstration of HAAg in a single stool specimen identifies an active case of hepatitis A. More commonly, documentation of hepatitis A is predicated upon the serologic demonstration of a significant increase in anti-HAV titer during the acute stage of the disease. Anti-HAV is present at the onset of jaundice, and the absence of antibody at this stage of the disease excludes HAV as the etiologic agent of the illness. The titer of antibody increases rapidly during the first 2 weeks of illness. After infection, anti-HAV is usually present in the serum for life. If titers are obtained late in the course of the disease, a high titer of anti-HAV will be present. The ability to document a fourfold rise in titer may not be possible. In this situation the diagnosis of acute infection can be confirmed by

the demonstration of anti-HAV antibody of the IgM class. Specific IgM antibodies are synthesized during the first 2–3 months of hepatitis A.

Hepatitis B

Detection of markers of hepatitis B, namely HBsAg, anti-HBs, anti-HBc, HBeAg, or anti-HBe, can be achieved by precipitation in gel, counterimmunoelectrophoresis, latex agglutination, passive hemagglutination by immunoenzymes, and radioimmune methods. The most sensitive method is RIA. The current commercial kits have excellent sensitivity and reproducibility. Recently, the enzyme immunoassay (EIA) has been adapted for HBsAg.

While the presence of HBsAg documents the diagnosis of hepatitis B infection, it does not address the issue of infectivity.

The presence or absence of IgM antibody to the core antigen of HBV (IgM anti-HBc) provides a means of distinguishing between acute infection and chronic disease. Almost all patients with acute hepatitis B have high titers of IgM anti-HBc at the time of initial examination, whereas chronic carriers of the virus have only low titers or no detectable IgM anti-HBc at all but will have high titers of IgG anti-HBc. The presence of hightiter IgM anti-HBc generally indicates the patient has acute hepatitis B (hepatitis Delta co-infection is not excluded), whereas a negative test in a HBsAg-positive patient with hepatitis should prompt the consideration of other possibilities, especially hepatitis delta superinfection or intercurrent non-A, non-B hepatitis. With respect to the diagnosis of acute hepatitis B, IgM antiHBc is arguably the best serologic marker.

Hepatitis C

A variety of tests are available for hepatitis C diagnosis. Tests that can detect antibody against the virus include the EIAs, which contain HCV antigens from the core and nonstructural genes, and the recombinant immunoblot assays (RIBAs), which contain the same HCV antigens as EIA in an immunoblot format. In addition, several polymerase chain reaction (PCR)-based assays for HCV RNA have been developed to detect the RNA virus directly.

Only about 70% of patients with acute hepatitis C develop detectable antibodies to HCV antigen within six weeks of the onset of signs or symptoms. The diagnosis of acute HCV infection may require follow-up testing at twelve weeks.

While serum ALT and other enzymes indicative of hepatocellular destruction are reasonable indicators of the presence of disease, they are poor indicators of activity. Over half of all viremic patients will have normal ALT levels. ALT levels are often normal or near normal even in patients with biopsy-proven advanced liver disease. As a consequence, normal ALT levels do not preclude the presence of chronic HCV infection.

Serologic testing for HCV is currently the only way of documenting infection or disease. The newer immunoassays for HCV, composed of multiple HCV specific antigens, have both sensitivities and specificity in the range of 95%. False-negatives occur due to the heterogeneity of the virus. Current EIAs are based on the predominant genotype of HCV found in US patients. False-positive results occur in patients with hypergammaglobulinemia and connective tissue disorders.

Recombinant immunoblast assay (RBA), which uses recombinant proteins derived from HCV, is used to confirm EIA results. This test contains four HCV-specific antigens blotted as separate bonds on a nitrocellulose strip. A confirmatory RBA test result demonstrates reactivity to two or more of these antigens. As with the EIA test, false-negative tests do occur. Patients infected with less common HCV genotypes are less likely to satisfy the diagnostic criteria required.

Direct detection of HCV viral genomic RNA can be done using PCR. This test is available as primarily a research tool. The presence of anti-HCV antibodies in human serum or plasma does not necessarily indicate on-going NANBH but may be a remnant of a past infection with the HCV. Levels of antibody are usually undetectable in early stages of an infection.

Anti-HCV antibodies appear as early as four weeks and as late as one year after infection. The mean delay between onset of hepatitis symptoms and seropositivity is 15 weeks. In acute post-transfusion hepatitis, the mean delay between transfusion (infection) and appearance of anti-HCV is 22 weeks. Once the antibodies develop, they persist for years. Unlike hepatitis B, the ‘window period’ is variable. When the diagnosis of hepatitis C is strongly suspected, sequential repeat testing for anti-HCV is recommended. The maior usefulness of the test is to screen out blood donors who could transmit HCV. A positive test for the presence of anti-HCV will assist in the diagnosis of individuals with recent or prior signs, symptoms and/or biochemical evidence of hepatitis. A negative test is of limited value.

False-positive reactions with the EIA for hepatitis C have been seen in some patients with hypergammaglobulinemia and in patients whose serum has been stored improperly or for a prolonged period. False-negative antibody studies in acute HCV disease are related mainly to the slow development of antibodies during convalescence.

To establish a diagnosis of perinatal/neonatal hepatitis C, virological testing requires the use of branched chain DNA (bDNA) amplification assay or PCR. These tests are required because passively transferred maternal antibodies against HCV can interfere with EIA tests. Infants born to HCV infected mothers should be tested before breast feeding is initiated or within twelve months of birth. If positive, the bDNA assay or PCR should be repeated between 12 and 15 months of age. After 15 months of age the infant can be monitored serologically using anti-HCV assay for indigenous antibody production indicative of HCV infection.

PASSIVE IMMUNOTHERAPY

Diagnostic evaluation for hepatitis C

A negative EIA test is sufficient to rule out infection. However, low-risk individuals with positive EIA tests should undergo supplementary RIBA testing. If the RIBA is negative, the anti-HCV EIA result is likely to have been a false positive, and the patient is unlikely to have hepatitis C. If the RIBA is positive, the patient can be asumed to have or to have had hepatitis C. These patients can benefit by testing for HCV RNA by PCR, the result of which will indicate whether the patient has ongoing viremia. A single positive assay for HCV RNA by PCR confirms HCV infection; unfortunately, a single negative assay does

not prove that the patient is not viremic or has recovered from hepatitis C. Follow-up testing for ALT levels and perhaps repeating the HCV RNA in the future may be needed.

Individuals with even mildly elevated ALT levels, with or without risk factors for hepatitis C, should be tested for anti-HCV by EIA and, if positive, the results confirmed by either supplemental RIBA or qualitative HCV RNA by PCR. Obviously anti-HCV testing is very helpful in all patients with clinical liver disease.

In patients presenting with biochemical or clinical evidence of liver disease (e.g. repeatedly elevated ALT levels), a positive EIA test is sufficient to diagnose hepatitis C infection, especially if risk factors are present. A qualitative HCV RNA test can be used for confirmation. If a patient is being considered for antiviral therapy, liver biopsy is of value to assess disease severity.

Testing for HCV RNA by PCR can be very helpful in initial diagnosis, but repeat testing over time is generally not helpful in managment of untreated patients; almost all remain viremic, and a negative result may merely reflect a transient fall of viral titer below the level of detection rather than permanent clearance. On the other hand, repeat testing for HCV RNA during antiviral therapy can be helpful because loss of HCV RNA with treatment is a strong predictor of a sustained beneficial response.

Liver biopsy is considered the gold standard for assessment of patients with chronic hepatitis. When combined with serial determinations of ALT levels, liver biopsy is very helpful in judging the severity or activity of the liver disease and the stage or degree of fibrosis. Liver biopsy is recommended before treatment to assess the grade and stage of disease and to exclude other forms of liver disease or complications (such as concurrent alcoholic liver disease, medication-induced liver injury, and iron overload). However, liver biopsy is expensive and is associated with some morbidity. Therefore, serial ALT and qualitative HCV RNA testing are recommended for monitoring patients under treatment.

Contraindications to treatment with interferon that must be carefully considered are history of major depressive illness, cytopenias, hyperthyroidism, renal transplant, and convincing evidence of autoimmune disease.

Data suggest a benefit from interferon treatment with higher clearance of HCV RNA in patients with acute hepatitis C. In light of these findings, interferon treatment of patients with acute hepatitis C could be recommended.

The adjunctive drug of most promise, at present, is ribavirin, an oral antiviral agent that, when used alone, reduces serum ALT levels in approximately 50% of patients. However, ribavirin by itself does not lower serum HCV RNA levels, and relapses occur in virtually all patients when therapy is stopped. Of greater promise are recent reports that the combination of interferon alfa and ribavirin leads to sustained virological response rates (40 to 50%) higher than for interferon alfa alone in 6-month clinical trials. Ribavirin has not been licensed or approved for use in hepatitis C by the Food and Drug Administration.

For pregnant patients with chronic active hepatitis due to HCV, general anesthesia is best avoided when cesarean section is indicated. Some neonatologists empirically administer immune globulin to the progeny of such gravida with high titer of HCV antibodies. Currently there is little scientific data to support or negate this approach. *In utero* transmission is an unexplored possibility.

Hepatitis A

The efficacy of immune serum globulin (ISG) for the prevention or modification of hepatitis A depends on the following:

(1) the degree and type of exposure;
(2) the dose of ISG and its antibody content; and
(3) the time interval between exposure and the administration of ISG.

Optimal passive immunization following presumed exposure requires the use of high-titered, HBsAg-negative ISG, administered in the shortest possible time after exposure. Different lots of ISG may vary as much as 16-fold in anti-HAV content. It will be imperative in the future for licensed lots of ISG to be marked as to anti-HAV titer.

Administration of ISG early in the incubation period of type A hepatitis is capable of modifying or arresting the infection. A dose of 0.02 ml/kg body weight affords effective protection for short-term exposure.

Pregnancy *per se* does not alter the recommendations for ISG prophylaxis. The administration of ISG is indicated following known exposure to HAV or in anticipation of entering an area where disease is endemic and intermittent exposure probable. Under most circumstances, protection is afforded by giving 0.01 ml ISG/lb of body weight (approximately 0.02 ml/kg). Larger doses provide longer lasting, but not necessarily more, protection and are indicated when an individual plans to reside in a high-risk area for a prolonged period. A dosage as high as 0.05 ml/lb every 5–6 months has been advocated.

Although HAV does not traverse the placenta, maternal infection immediately prior to delivery unless appropriate isolation procedures are instituted and ISG is administered, raises the possibility of neonatal dissemination of disease from mother to infant in the postpartum period.

Hepatitis B

The ability to answer the question as to the efficacy of standard ISG as prophylaxis against hepatitis B has been largely negated by the significant variation in anti-HBs from lot to lot. Most lots of standard ISG have contained low or undetectable levels of anti-HBs. The development of a hepatitis B immune serum globulin (HBIG) preparation with an anti-HBs titer about 25000–50000 times higher than that of standard ISG has demonstrated that partial efficacy may be achieved through passive immunization.

HBIG should be given immediately, at a dose of 0.06 ml/kg body weight, to individuals who are exposed by a contaminated needle or by contact with infective blood splashed onto a mucous membrane or a skin cut, or to those who have had intimate physical contact with a person who has hepatitis B infection. This dose should be repeated in 28 days. An individual given a blood transfusion that, in retrospect, is discovered to be infected with HBsAg may be given large doses of HBIG (0.5 ml/kg). Large doses of HBIG or high-titered plasma are of no value in the treatment of on-going infection.

In infants whose mothers had hepatitis B during pregnancy or have persistent antigenemia, the probability of ensuing postnatal hepatitis tends to be influenced by the presence or absence of other viral markers in the mother. The attack rate of hepatitis B in

infants born to mothers with a persistence of HBsAg, HBeAg, and anti-HBc usually exceeds 50%. Large doses of HBIG are recommended for these infants. The probability of hepatitis B in infants born to mothers with a persistence of HBsAg and anti-HBe is usually less than 10%. The accumulated evidence to date indicates that HBsAg-positive and HBeAg-positive blood is highly infectious, whereas HBsAg-positive, anti-HBe-positive blood is minimally infectious. The many known ways to limit dissemination or acquisition of infection must not be neglected. With effective surveillance of patients and personnel exposed to hepatitis B, proper washing of hands, and stringent aseptic technique for eliminating HBs-positive blood products, the potential for spread of HBV disease is reduced.

ACTIVE IMMUNIZATION

Hepatitis A virus

The inability to cultivate HAV in a suitable cell line and to produce the large quantities of antigen that are needed for the preparation of a vaccine has thwarted vaccine development to date.

Hepatitis B virus

The demonstration that immunization with purified viral coat protein, HBsAg, leads to the production of protective surface antibodies introduced the possibility of using purified 22 nm spherical hepatitis B antigen in vaccines, in lieu of whole virus.

RECOMBIVAX HB®: Hepatitis B vaccine and ENGERIX-B®

RECOMBIVAX HB® [Hepatitis B vaccine (recombinant)] and ENGERIX-B®, are non-infectious subunit viral vaccines derived from HBsAg produced in yeast cells. A portion of the HBV gene coding for HBsAg is cloned into yeast and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain. The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

Infants born to HBsAg-positive mothers are at high risk of becoming chronic carriers of HBV and of developing the chronic sequelae of HBV infection. Well-controlled studies have shown that administration of three 0.5 ml doses of HBIG starting at birth is 75% effective in preventing establishment of the chronic carrier state in these infants during the first year of life. Protection can be transient, whereupon the effectiveness of the HBIG would decline thereafter. Results from clinical studies indicate that administration of one 0.5 ml dose of HBIG at birth and three 20 μg (1.0 ml) doses of hepatitis B vaccine, the first dose given within one week after birth, was 85–93% effective in preventing establishment of the chronic carrier state in infants born to HBsAg- and HBeAg-positive mothers.

The immunization regimen consists of 3 doses of vaccine:

• 1st dose: at elected date

• 2nd dose: 1 month later
• 3rd dose: 6 months after the first dose.

The protective efficacy of hepatitis B vaccine has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg. In a clinical study of infants who received one dose of HBIG at birth followed by the recommended three dose regimen of hepatitis B vaccine, efficacy in prevention of chronic hepatitis B infection was 94% in 93 infants at six months and 93% in 57 infants at nine months as compared to the infection rate in untreated historical controls. Significantly fewer neonates became chronically infected when given one dose of HBIG at birth followed by the recommended three dose regimen of hepatitis B vaccine when compared to historical controls who received only a single dose of HBIG. Testing for HBsAg and anti-HBs is recommended at 12–15 months of age. If HBsAg is not detectable, and anti-HBs is present, the child has been protected. The recommended treatment regimen for infants born of HBsAg-positive mothers is shown in Table 12.4.

THERAPY

Hepatitis C

There is no established therapy for chronic hepatitis C. A multi-center, randomized, controlled trial recently demonstrated that treatment with 3 million units of recombinant alpha interferon three times weekly for six months is associated with normalization or near-normalization of hepatic enzyme levels in 46% of patients, compared to 28% of patients receiving lower doses of interferon and 8% of those receiving no interferon.

Although several different forms of interferon have been evaluated in the treatment of patients with chronic hepatitis C, the bulk of available evidence pertains to the alpha interferons (interferon alfa). The efficacy of interferon alfa therapy currently is defined biochemically as normalization of serum ALT and virologically as loss of serum HCV RNA. Therefore, serial ALT testing is recommended for monitoring patients during treatment to document biochemical responses, and testing for HCV RNA by qualitative PCR is recommended at selected time points to document virological responses.

Many therapeuticians obtain a liver biopsy before initiating therapy with interferon. Laboratory tests that should be obtained before starting therapy include liver chemistries (serum ALT, bilirubin, albumin, prothrombin time), complete blood count (CBC) with differential and platelet count, antinuclear antibodies, thyroid stimulating hormone, serum HCV RNA, and glucose. Monitoring during therapy should be done at 2- to 4-week intervals with serum ALT and CBC. Both serum ALT and serum HCV RNA testing should be done after 3 months to assess whether the patient is responding to therapy. This should be repeated at the end of therapy to document end-of-treatment response. Follow-up testing with serum ALT and serum HCV RNA should be done 6 months after therapy is stopped to determine whether there has been a sustained response.

Three months after beginning an initial course of therapy, patients who are unlikely to respond to that dosage and freuency can be identified by persistent elevation of serum ALT levels and presence of HCV RNA in the serum. In this situation, therapy should be discontinued because the likelihood of future response is extremely low. If either HCV

RNA is negative or ALT levels are normal (or both), therapy should be continued for 12 months.

The important factors associated with a favorable response to treatment include HCV genotype 2 or 3, low serum HCV RNA level (less than 1000000 copies/ml), and absence of cirrhosis.

Flulike symptoms (fever, chills, malaise, headache, arthralgia, myalgia, tachycardia) occur early in the majority of patients who receive interferon but generally diminish with continued therapy. Later side effects include fatigue, alopecia, bone marrow suppression, and neuropsychiatric effects such as apathy, cognitive changes, irritability, and depression. Relpase of drug and/or alcohol abuse may occur. Nocturnal administration of interferon reduces the frequency of side effects, and the flulike syndrome is ameliorated by pretreatment with acetaminophen. A reduction in interferon dosage is required in 10 to 40% of patients because of side effects, and treatment must be discontinued in 5 to 10%. Higher dosages tend to be associated with higher rates of side effects.

Chronic hepatitis C

Interferon is indicated for treatment of chronic hepatitis C in patients 18 years or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody-positive. Interferon therapy is not recomended for patients with decompensated liver disease, pre-existing psychiatric conditions, autoimmune liver disease, or suppressed immune response following organ transplantation.

Alfa-2b interferon is the only effective treatment to date for hepatitis C. Parenteral administration of three million units, three times a week, for six months will result in normal serum alanine aminotransferase during therapy but approximately half of these patients relapse within six months. For those patients with chronic hepatitis C who do not respond to interferon alfa regimen, the only possible alternative treatment is orally administered ribavirin.

For pregnant patients with chronic active hepatitis due to HCV, general anesthesia is best avoided when cesarean section is indicated. Some neonatologists empirically administer immune globulin to the progeny of such gravida with high titer of HCV antibodies. Currently, there is little scientific data to support or negate this approach.

Patients most likely to respond to interferon alfa are those:

(1) without cirrhosis;
(2) with evidenced chronic hepatitis/periportal inflammation on biopsy;
(3) with low HCV-RNA levels;
(4) with low serum ferritin;
(5) with low gamma-glutamyl transpeptidase; and/or
(6) with HCV genotype 2.

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13
Herpes simplex viruses, types 1 and 2 (HSV-1, HSV-2)

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The herpesviruses are composed of a single molecule core of double-stranded DNA, an icosahedral structure with 162 capsomers, a granular zone, and a lipid envelope which contains predominantly viral-specific glucoproteins. As a characteristic of the herpesvirus group, virus replication occurs in the cell nucleus. Six to eight hours after infection, synthesis and assembly of virus particles can be observed with the electron microscope. A basophilic Feulgen-positive mass centrally displaces the nuclear chromatin. Electron microscopy reveals this viral DNA core to be surrounded by a protein coat. There is a subsequent movement of the virus particle from the nucleus to the cytoplasm. This is paralleled by morphologic changes in the intranuclear inclusion body. The central ovoid intranuclear inclusion body loses both its basophilia and its affinity for DNA stains. The lesion is characterized by an eosinophilic, irregular central intranuclear inclusion body rimmed by peripheral fragments of chromatin at the margins of the nuclear membrane (Figure 13.1). The virion obtains its final envelope from the nuclear membrane.

The DNA viruses of the herpesvirus group do not undergo immune elimination. Despite the presence of specific antibody, they persist as latent viruses. Recrudescence of herpes simplex virus (HSV) replication may be triggered by a variety of exogenous factors (e.g. cold, fever, intense sunlight, emotional stress, menstruation). Recurrent infection occurs in the presence of complement-fixing and neutralizing antibodies and is rarely associated with serologic evidence of a boostertype effect. In contrast to primary infection, it is unassociated with systemic symptoms and most often occurs at the site of initial infection.

Two types of herpesvirus can be identified on the basis of divergent biologic properties and are designated types 1 and 2 (HSV-1 and HSV-2; Table 13.1). They can also be differentiated by minor differences in antigenic composition and biochemical characteristics. Although they are distinct, the degree of sharing of antigenic determinants between the type 1 and 2 viruses results in cross-reacting antibodies capable of extensively neutralizing the heterologous virus type.

Initial contact with HSVs usually occurs early in childhood and involves HSV-1. Less than 10% of primary infections with HSV-1 are clinically overt.

HSV-1 is the causative agent for most nongenital herpetic lesions: herpes labialis, gingivostomatitis, and keratoconjunctivitis. Infection of the female genital tract by HSV-1 may occur at this time; however, the virus can often be simultaneously cultured from nongenital sites, suggesting that genital involvement is most often a secondary phenomenon.

FEMALE GENITAL TRACT INVOLVEMENT

Approximately 30% of the female population in the United States is infected with HSV-2 as determined by using sensitive HSV type specific antibody studies performed on collected and stored sera. Herpes simplex virus of the genital tract is one of the most common viral sexually transmitted diseases (STDs) with an estimated 40 million men and women infected with genital herpes. An average of 500000 new cases of genital herpes is acquired each year. The genital tract of the female patient can be infected with HSV type 1 or type 2 virus. In the United States the majority of genital infection is

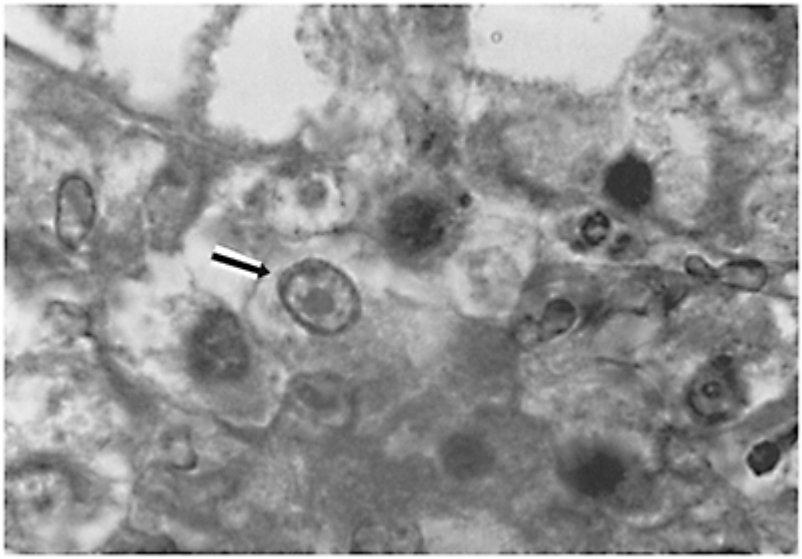

Figure 13.1 Characteristic mature intranuclear inclusion body (arrow) due to HSV-2 within tissue (H&E, ×1000)

Table 13.1 Major distinguishing biologic and epidemiologic characteristics of type 1 and type 2 herpes simplex viruses

Characteristic	***Type 1***	***Type 2***
Pock size on chorioallantoic membrane of embryonated eggs	Small	Large
Plaques in chick embryo tissue cultures	None	+++
Neurovirulence for mice	++++	+
Sensitivity to idoxuridine (5-iodo-2'-	+++	+

deoxyuridine)		
Principal sites of viral replication	Nongenital	Genital
Group in which genital involvement occurs	Prepuberty; adolescence	Postpuberty; sexually active years
Principle mode of dissemination	Hand-to-mouth	Venereal

from HSV-2 virus. Up to 30% of first episode cases of genital herpes are caused by HSV-1. The vast majority of primary genital infections are caused by HSV-2.

Primary infection of the genital tract can produce clinical disease with symptoms or can be subclinical. Five percent of reproductive age women will give a history of genital herpes virus infection. Genital infection with HSV is associated with the age of the patient, years of sexual activity, race, one or more episodes of other genital infections, lower annual family income and multiple sex partners. After clinically apparent primary genital herpes infection almost all patients will experience recurrences; however recurrences with HSV-2 tend to be much less frequent.

Type 2 antibodies usually appear first about the time of puberty and exhibit a significant increase during the

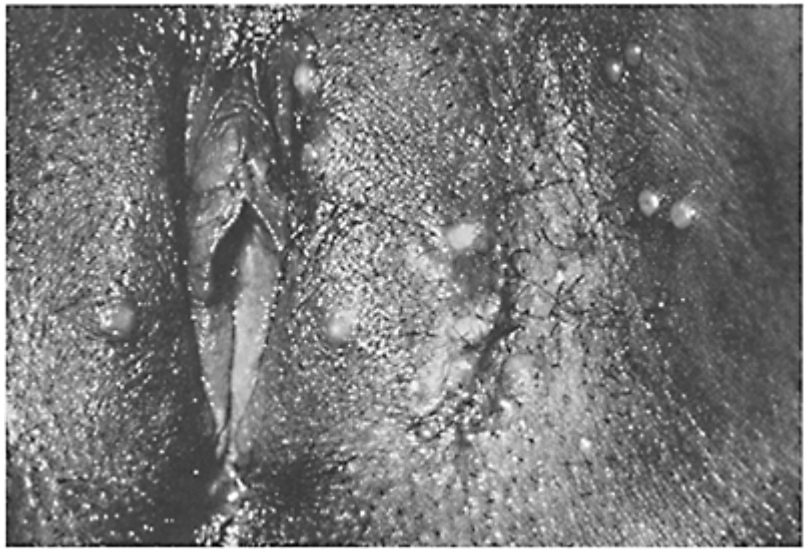

Figure 13.2 Vesicular and vesiculopustular lesions characteristic of genital herpes

prime reproductive years. The greatest incidence of overt type 2 infection occurs in women in their late teens and early twenties.

HSV-2 is recovered predominantly from the female genital tract. Epidemiologic data strongly support the thesis that dissemination of the type 2 strain is primarily but not exclusively contingent on venereal transmission. The incidence of specific antibody approaches 100% among prostitutes. Following exposure to males with active herpetic lesions of the genitalia, 50–90% of susceptible sexual partners develop infection.

Primary infection

Primary genital infection due to HSV-2 may be asymptomatic or may be associated with severe symptoms. In primary vulvovaginitis the genital lesions occur on the vulva, vagina, cervix, or all three between 2 and 14 days following exposure to infectious virus (Figure 13.2). Like those in primary herpes labialis. the lesions are multiple and larger than those observed in recurrent disease or in those who have had prior infection with HSV-1. At this time, patients usually experience vaginal discharge, discomfort, and pain. The mucocutaneous lesions are prone to trauma. The initial vesicles rupture and may become secondarily infected (Figure 13.3). They subsequently appear as shallow, eroded, painful ulcers covered by a shaggy white membrane. Regional lymphadenopathy is readily demonstrated as the consequence of virus replication in the sites of lymphatic drainage as well as nodal stimulation by secondary bacterial infection.

Whereas local symptoms of dysuria, soreness of the vulva and vagina, dyspareunia, and a sudden increase of discharge are common in both primary and recurrent infection, systemic symptoms (malaise, myalgia, and fever) are virtually restricted to primary herpetic infection (Table 13.2). These symptoms reflect the viremia engendered during primary infection. The lesions tend to persist 1–3 weeks without therapy. However, when secondary bacteria or mycotic infection is not treated, the lesions may persist for 2–6 weeks (Figure 13.4).

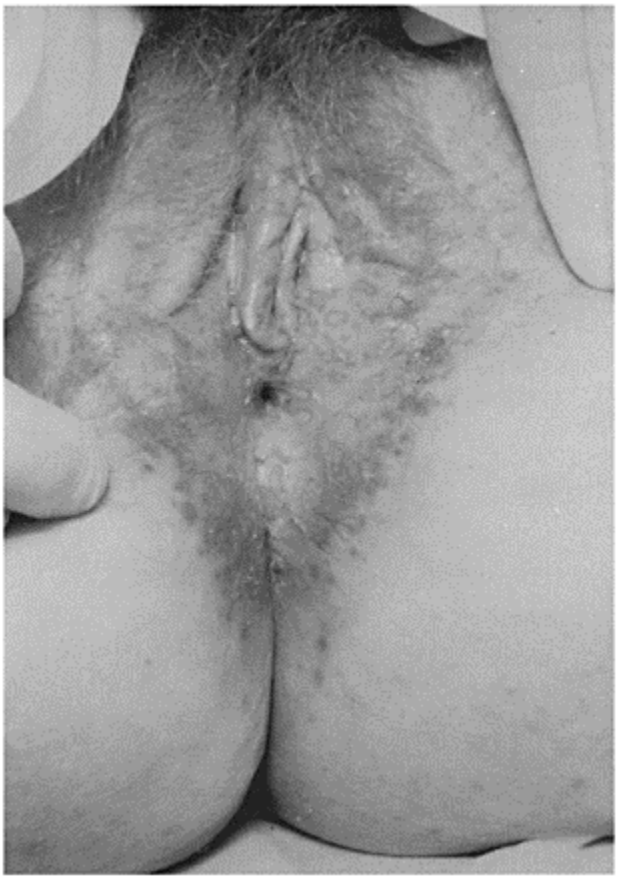

Figure 13.3 Classical primary herpetic vulvovaginitis. Note the multiplicity of the ulcers and the fact that the majority of them have become secondarily infected.

Primary herpetic infection may occur on the cervix. The appearance of extensive cervical involvement may mimic that observed with squamous cell carcinoma of the cervix. Significant symptomatic and subclinical shedding can be found from the lower genital tract of the women. During the first three months after healing of primary genital HSV-2 lesions subclinical cervical and vulvar shedding was more frequent. Asymptomatic shedding occurs around the time of symptomatic recurrences.

Recurrent infection

Confinement of the ulcers to one area of the vulva, vagina, or cervix is more common in recurrent forms of the disease. The ulcers tend to be limited in size and number. Cervical involvement may occur as a diffuse cervicitis or as a single large ulcer. Local symptoms predominate over systemic symptoms, with increased vaginal discharge or pain being the usual presenting complaint. In certain women it can be demonstrated that once it is involved, the genital tract is the site of intermittent virus replication. Virus shedding without a lesion (subclinical shedding) can occur from the vulva and cervix intermittently in subsequent years after primary infection. The titer of virus is significantly reduced compared to the level of recoverable virus when clinically overt lesions are present.

Subclinical shedding of virus lasts an average of one and one-half days and the quantity of virus is lower, however a susceptible partner can acquire this virus during times of subclinical shedding. Shedding of virus without any symptoms or signs of clinical lesions (subclinical shedding) makes this viral STD difficult to control and prevent. Patients will experience recurrent disease after clinical or subclinical primary HSV genital infection. Recurrences of genital HSV infection can be symptomatic or subclinical and there is significant variation from patient to patient in the frequency, severity, and duration of symptoms and viral shedding. Young adult women tend to acquire the first episode of genital herpes between the ages of 20 and 24 years. Direct contact with an individual who is infected is required for the transmission of this viral infection. This maybe genital to genital contact or contact of the genital tract from an area that is infected with HSV such as oral to genital contact. Direct sexual contact is the most common source of genital HSV transmission to women.

Diagnosis

Maternal herpes infection may be documented in several ways. Being DNA viruses, the HSV produce histologic stigmata indicative of virus replication. Papanicolaou smears of a given lesion may demonstrate large multinucleated cells containing eosinophilic intranuclear inclusion bodies (Figure 13.5). Cytological tests have a maximum sensitivity of 60–70% when dealing with overt clinical disease. Both the Papanicolaou and Zanck smears are poor screening procedures. The presence of

Table 13.2 Clinical differences between primary and recurrent vulvovaginitis due to herpes simplex virus type 2

Signs or symptoms	***Primary***	***Recurrent***
Number of lesions	Multiple	Scattered 1 to 3
Location of lesions	Tend to involve both labia and vagina; cervix may be concomitantly involved	Limited involvement of vulva, vagina, or cervix
Size of lesions	Variable; tend to be larger than those observed in recurrent disease	Tend to be smaller

Inguinal adenopathy	Present	Usually absent
Viremia	Occurs	Absent
Systemic symptoms (malaise, myalgia, fever)	Present*	Absent
Local symptoms (dysuria, itching, dyspareunia)	Present	Present
Specific antibody titer	Greater than fourfold rise observed between pre- and postconvalescent sera	Usually no significant change

*Only in the absence of preexisting antibodies to herpes simplex type I.

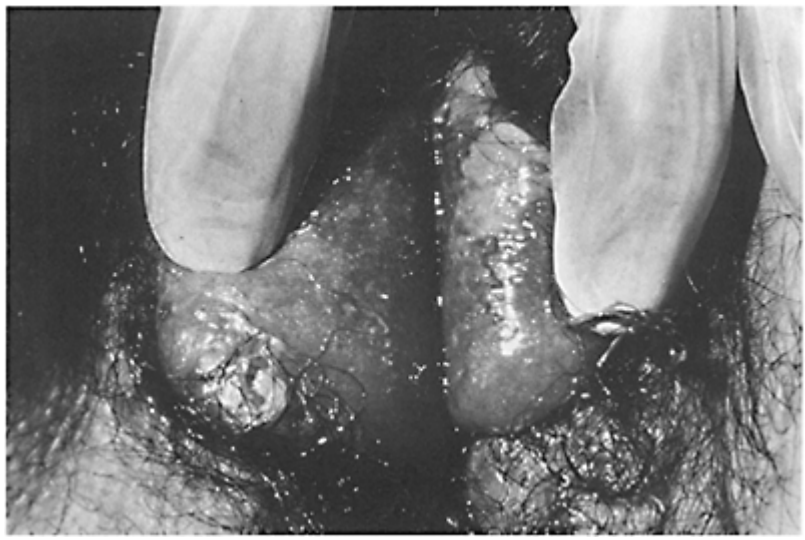

Figure 13.4 Painful herpetic ulcers with a shaggy white membrane and marked bilateral labial edema as a consequence of secondary bacterial infection. (Courtesy of MS Amstey, MD, Rochester, NY)

multinucleated giant cells is predominantly a phenomenon of herpetic involvement at free surfaces, as opposed to the single intranuclear inclusion body observed within organ tissues. Biopsy in conjunction with cytologic analysis of a cell preparation from the lesion very often leads to a diagnosis, even in the absence of virus isolation studies.

Isolation of virus by cell culture remains the standard and the most sensitive test for the detection of infectious herpes virus from clinical specimens. Numerous

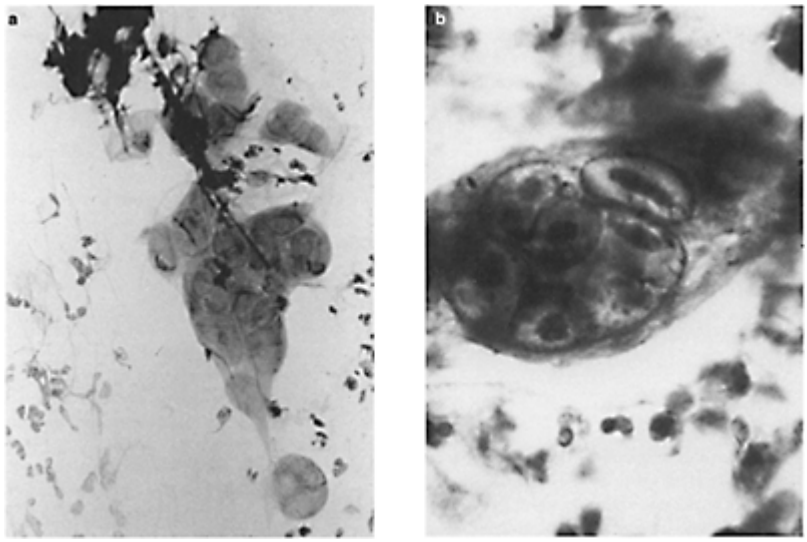

Figure 13.5 Multinucleated giant cells exhibiting intranuclear inclusion bodies. Due to herpes simplex type 2 virus found in a cytological smear of a herpetic ulcer. (a) The photomicrograph is from a more active lesion. The classical irregular eosinophilic intranuclear inclusion body is not present.The nuclei exhibit gigantism with a ground-glass background in which is scattered chromatin fragments. (Papanicolaou stain, ×610). (b) The photomicrograph demonstrates a mature multinuclear giant-cell. Each nucleus has a discrete central intranuclear inclusion body surrounded by a halo. (Papanicolaou stain, ×1200).

factors in sampling and transport of the specimen determine the sensitivity of this technique. False-negative cultures are not uncommon in patients with recurrent infection or healing lesions.

Newer more sensitive techniques such as polymerase chain reaction (PCR) and hybridization methods are largely replacing virus isolation techniques.

Early first episode ulcers yield virus in 80% of patients, whereas ulcers from recurrent infections are less likely to be culture-positive and only 25% of crusted lesions contain recoverable virus. In culturing for HSV, overt lesions that are not in the ulcerated state should be unroofed and the fluid sampled. Virus isolation can be readily achieved in many primary or continuous human tissue culture cell lines.

The newly available serologic type-specific IgG-based assays can distinguish infection between HSV type I and type 2 antibodies. These new tests have excellent sensitivity (80–98%) and specificity (>96%) in comparison with Western blot assay; however, early in the course of infection, false-negative tests may occur. The older nonspecific antibody tests are of limited value owing to the frequency of cross-reacting antibodies to heterologous virus. IgM antibody test for HSV-1 and HSV-2 should not be used to diagnose acute infection.

HSV-2 is considered to reside primarily in the genital tract. A demonstration of HSV-2 type specific antibodies by a glycoprotein gG based assay is deemed evidence of genital tract infection.

If the acute-phase serum has nondetectable or very low titer and the convalescent serum obtained 10–14 days after the onset of clinical disease demonstrates a fourfold or greater rise in the titer, the diagnosis of primary infection can be made. The presence of an antibody titer in the initial specimen obtained at the onset of disease, and the failure of the titer to exhibit a fourfold or greater rise in the convalescent specimen or the presence of IgM specific antibodies argues strongly for recurrent infection.

Therapy

Numerous treatment options are available to the clinician to treat patients with genital herpes. These compounds are nucleoside analogues and they selectively inhibit viral replication and produce little or minimal effects on the cell. Acyclovir was the first drug developed in this classification. This drug possessed a high safety profile along with being selective against herpesvirus infected cells. Further advances with antiviral therapy have focused on greater bioavailablity and therefore better absorption and higher plasma levels of compound with fewer daily doses of medication.

Acyclovir

Acyclovir was the first purine nucleoside analogue with a new and selective activity against virus infected with HSV-I and-2. HSV viral DNA replication is stopped and the drug acts selectively against a viral coded protein, thymidine kinase. The drug has shown to be very safe with few side effects. However it has poor oral absorption. Only approximately 20% of an oral dose is absorbed. The Food and Drug Administration (FDA) has approved acyclovir for the treatment of primary genital herpes, treatment of episodes of recurrent disease and for daily treatment for suppression of outbreaks of recurrent genital herpes.

Approximately 3% of isolates obtained from healthy patients demonstrate *in vitro* resistance to acyclovir. The frequency of *in vitro* resistance has not changed from that prior to its introduction. The demonstration of *in vitro* resistance has only rarely been associated with clinical failure in immunocompetent individuals. Foscarnet, a

phosphonate viral DNA inhibitor or cidofovir, an acyclic nucleoside phosphonate, have been used in infected AIDS patients with acyclovir-resistant isolates of herpes virus.

Valacyclovir

This newer antiviral is acyclovir with a valine ester. This drug is only for oral administration and because there is an enzyme in the gut that cleaves the valine, the bioavailability is 3 to 5 times greater than oral acyclovir. The safety profile is that of acyclovir with a less frequent dosing schedule. The FDA has approved valacyclovir for the treatment of primary genital herpes, treatment of episodes of recurrent disease and for daily treatment for suppression of outbreaks of recurrent genital herpes.

Famciclovir

Famciclovir is a prodrug of penciclovir. Bioavailability is good but there is less clinical long term use than acyclovir. Famciclovir requires less frequent dosing than acyclovir but more frequent dosing than valacyclovir.

All cases of primary genital herpes should be treated with antiviral medication. Currently, the FDA has approved acyclovir, valacyclovir, and famciclovir for the treatment of primary genital herpes, recurrent episodes of genital herpes (episodic therapy) and daily suppressive therapy of this disease. There is greater bioavailability of the newer agents valacyclovir and famciclovir so they may require a less frequent dosing schedule to get as good therapeutic benefit as acyclovir. Acyclovir treatment of primary genital herpes infections reduces viral shedding, reduces pain and heals lesions statistically significantly faster than placebo. Antiviral therapy should be administered as early in the course of the disease as possible for the greatest therapeutic benefit. With all these antiviral medications, therapy for the primary infection does not alter the natural history of genital herpes nor alter the frequency of recurrent disease. Newer information concerning symptomatic and asymptomatic shedding within the first three to six months post primary infection may direct the clinician that in selective patients continued therapy after the first ten days may be indicated. Therapy for the initial months past primary infection appears to significantly suppress symptomatic and asymptomatic shedding.

The clinician can select patient initiated episodic or daily suppressive therapy to control this disease in immunocompetent patients. All three medications have been studied and have received approval for these forms of therapy. Patient initiated episodic therapy can be effective in limiting each episode of recurrent disease but this mode of therapy does not prevent recurrences. Famciclovir has been shown to be effective in treating genital herpes with episodic therapy as compared to placebo. Valacyclovir compared to the standard dose of acyclovir has been tested in more than 2500 patients with self initiated episodic treatment for recurrent genital herpes. Valacyclovir is as effective as acyclovir in treating genital herpes episodically. In 50% of patients that have taken valacyclovir early in the prodromal phase it appears to prevent lesion development.

With the high frequency of recurrent disease in patients who acquire genital herpes daily suppressive therapy is a management mode that may benefit many patients. Antiviral therapy would be justified in patients after initial therapy for primary infection to reduce the increased symptomatic and asymptomatic shedding after primary infection.

A long term safety and efficacy study has recently been concluded in which more than 1140 immunocompetent patients with frequent recurrences of genital herpes (more than 12 episodes per year) were treated with acyclovir for the first ten years of the study and then valacyclovir in the eleventh year. Goldberg *et al.* summarizes the first five year data from that study. There is a statistically significant reduction in recurrent disease when acyclovir is used at 400 mg twice a day, There was a 75–90% reduction in recurrent disease in each three month quarter over the five year period. This long term study provides major insight and information concerning suppressive therapy. Adverse reactions to the medication were minimal and after the first year less than 2% of patients reported any one side effect. Nausea, diarrhea, headache and rash were seen during the study. Fife *et al.* showed that six years of continuous daily acyclovir suppressive therapy did not produce the emergence of acyclovir resistant isolates in immunocompetent patients. Approximately 3% of patients required a higher dose to control symptoms then the standard dose of 400 mg acyclovir twice a day. This study has continued for a total of 11 years and the data was recently reported at a national clinical meeting.

Suppresive therapy

Suppressive therapy can reduce the frequency of genital recurrences by 70–80% among individuals with frequent recurrences (6 or more per year).

Daily oral acyclovir therapy not only significantly reduces symptomatic recurrences but also suppresses subclinical viral shedding. Valacyclovir therapy of 500–1000 mg orally once day, famciclovir 250 mg orally twice a day is effective in suppressing recurrent genital herpes. Patients on long term suppressive therapy with oral acyclovir 400 mg twice a day can be changed to valacyclovir 500 mg once a day and maintain the safety and effectiveness of this therapy. Valacyclovir 500 mg once a day may be less effective than its higher dose or acyclovir dosing regimens in women who experience ten or more outbreaks in a year.

Recently, daily valacyclovir (500 mg) suppressed overt acquisition of HSV-2 in susceptible sexual partners. Overall acquisition, symptomatic and asymptomatic, was reduced 48% in the valacyclovir group compared to the placebo group.

HERPES IN PREGNANCY

Problems in distinguishing primary and recurrent genital herpes

In the absence of systemic symptomology, the distinction between primary and secondary herpetic

Table 13.3 Uses of antiviral therapy

For the **treatment of initial genital herpes infections in nongravida,** the recommended adult dosage of oral acyclovir is 200 mg every 4 hours while awake (5 times daily) for 7–10 days, or until clinical resolution occurs (initiated within 6 days of onset of lesions), or acyclovir 400 mg orally three time a day for 7–10 days or valacyclovir one gram orally twice a day for 7–10 days, or famciclovir 250 mg orally three times a day for 7–10 days.

For the **intermittent treatment of recurrent episodes,** the recommended adult dosage of acyclovir is 200 mg every 4 hours while awake (5 times daily) for 5 days or, alternatively, 800 mg twice daily for 5 days (initiated within 2 days of onset of lesions); of fanciclovir is 125 mg twice a day; of valacyclovir is 500 mg twice a day for five days.

For **chronic prophylaxis of recurrent episodes,** the recommended adult dosage of acyclovir is 200 mg 2–5 times daily or 400 mg twice daily; of famciclovir is 125 mg twice daily; and valacyclovir 500 mg once a day for patients with nine or less recurrences a year, 250 mg twice a day or 1000 mg once for women who experience more than nine episodes a year.

infection appears to be more difficult than previously assumed. Henseleigh *et al.* evaluated serologically and virologically 23 women with severe first clinical outbreak of genital herpes in the second and third trimester of pregnancy. They were classified as having true primary (no HSV type 1 or type 2 antibodies), nonprimary (heterologous HSV antibodies present), or recurrent (homologous antibodies present) infections. Only one of 23 women with clinical illnesses consistent with primary genital HSV infections had serologically-verified primary infection. This primary infection was caused by HSV type 1. Three women had nonprimary type 2 infections, and 19 women had recurrent infections.

This report demonstrates the need for careful serological evaluation of all cases of presumed first episode of genital herpes in pregnant women. In the absence of homologous and heterologous antibodies, the risk of congenital infection exists. Recurrent herpes may not be associated with vertical transmission unless a uterine site of reactivation is involved.

Disseminated maternal herpetic infection and pregnancy

Disseminated herpetic infection in an adult is distinct from herpetic encephalitis, although the latter may occur as part of the widespread organ system involvement. Disseminated disease in adults is thought to represent primary infection in a partially immunocompromised host, whereas herpetic encephalitis functions independent of systemic humoral or cellular immunity.

There are several patient populations in whom disseminated disease may occur: neonates, immunocompromised adults, particularly individuals with thymic dysplasias, and pregnant women. Disseminated herpetic infection in pregnancy is an extremely rare event. The manifestations of systemic dissemination in pregnancies tends to be viscerotropic rather than neurotropic. Its principal presentation is that of a fulminating hepatitis. Herpetic hepatitis is extremely rare, with a maternal mortality rate of 43%. Classically, disease occurs in the third trimester. Often there is viral-like prodromal illness in association with vulvar or oropharyngeal vesicular or vesiculo-pustular lesions. Despite elevated liver enzymes, most of the cases are anicteric. In some cases, no clinically overt site of primary herpetic infection can be identified. Chatelan *et al.* identified 14 cases in the literature. Of the 14 patient reported, 6 died. Four patients treated with parenteral acyclovir survived and 2 of the patients treated with the antiviral agent vidarabine also survived; however, 5 of 7 patients who did not receive antiviral therapy died.

Herpetic hepatitis should be included in the differential diagnosis of hepatic dysfunction in the third trimester. Any pregnant patient with primary infection in the third trimester should be closely watched for any evidence of disseminated disease. In the absence of herpetic lesions elsewhere, a diagnosis can be inferred by the demonstration of characteristic intranuclear inclusion bodies within a liver biopsy specimen. Once the diagnosis is made, acyclovir should be initiated to reduce maternal mortality

In every case, dissemination has occurred in the late second and third trimester at a time when maternal T-cell function is partially compromised. Both type 1 and 2 viruses have been isolated from gravidas with disseminated disease in pregnancy.

Fetal considerations: infection and fetal wastage

Preliminary data indicate a threefold increase in the rate of abortion following primary maternal genital infection with HSV early in pregnancy. The probability of abortion appears to be directly related if the maternal infection is primary. It has yet to be determined whether this increased fetal wastage is related to infection of the conceptus or is secondary to the maternal response to disease.

Congenital infection

During gestation, primary herpetic infection, in the absence of cross-protecting antibodies, theoretically may result in hematogenous dissemination of the virus to the conceptus.

Congenital herpetic infection can affect organogenesis or may produce visceral disease. *In utero* infection in the first 12–14 weeks of gestation may produce a cluster of anomalies clinically indistinguishable from those caused by the cytomegaloviruses. Chalhub *et al.* reported a case of a premature neonate with microcephaly and periventricular calcifications, bilateral lenticular opacities, and extensive hepatomegaly with secondary dystrophic calcification, who did not develop overt evidence of characteristic herpetic infection until day five. The fetal membranes ruptured 30 minutes before parturition. At necropsy the infant had characteristic lesions involving the brain, liver and adrenals. Eosinophilic Cowdry type A intranuclear inclusion bodies were present in hepatocytes adjacent to areas of bland necrosis and dystrophic calcification. Predicated upon the clustering of ocular lesions, microcephaly with dystrophic periventricular calcification and hepatosplenomegaly, this case could have been attributed to the cytomegalovirus. Similarly, an increased rate of premature births had been found in infants whose mothers had genital infection after the 20th week of pregnancy. This was particularly true with primary maternal herpetic vulvovaginitis.

The limited perception of the ability of HSV to cause disease *in utero* has been a partial function of the criteria used to define congenital infections. The rigid adherence to documented herpetic infection present at birth and/or within 24 hours of rupture of the fetal membranes had effectively excluded a significant number of cases. In the absence of well established placental or fetal pathology which clearly antedated potential access of the virus to the products of conception by means of ascending infection, the cases of congenital herpes reported by Von Herzen, and Benirschke, Altshuler, and Witzleben and Driscoll could have been challenged. Gagnon reported a case of what typically would

have been considered a case of neonatal disease developing on the fifth day of life. Had umbilical cord blood and placenta not been cultured for virus at the time of delivery, parturitional acquisition of disease would have been inferred. Similarly, Pettay described a case of overt acute neonatal disease which developed on the sixth day of life; however, HSV-2 had been recovered from an amniotic fluid specimen one week prior to parturition and at a time when the fetal membranes were intact.

The mucus plug of pregnancy and the presence of intact fetal membranes are a formidable barrier to ascending viral infection; however, once dissolution of the membranes occurs, the herpes viruses can obtain direct access to amniotic fluid and/or the fetus without ensuing vaginal delivery. For the term congenital herpetic infection to imply vertical hematogenous dissemination from the mother to the fetus, disease must develop within the shortest known incubation period required to induce overt disease in experimental animals from rupture of the fetal membranes or a virally induced effect on organogenesis must be identified in fetuses or neonates with documented herpetic infection. The criteria which can be used to make the diagnosis of congenital infection due to the HSVs include:

(1) documented herpetic infection present at birth and/or within 24 hours of rupture of the fetal membranes (Figure 13.6);
(2) effects of herpetic infection on organogenesis which antedate dissolution of the fetal membrane;

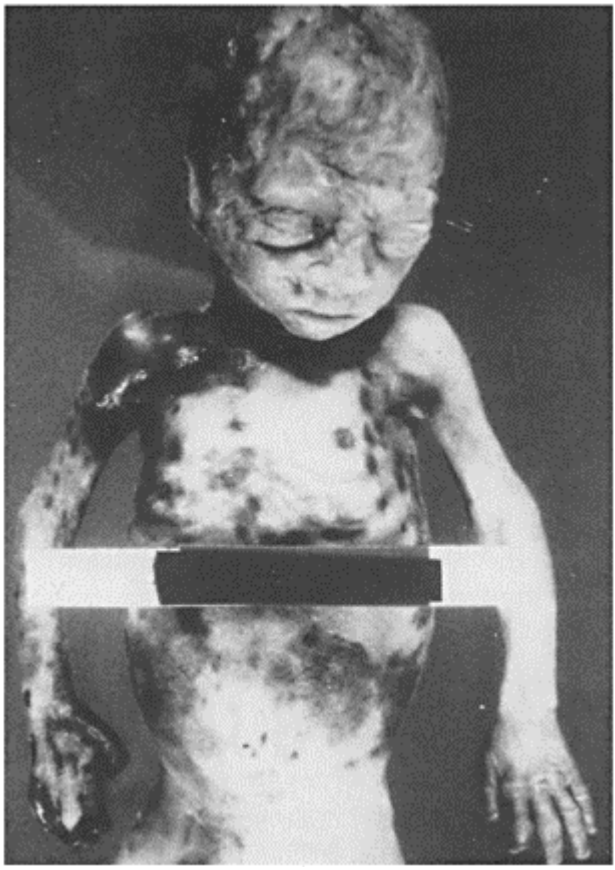

Figure 13.6 Fetus aborted at 28 weeks who demonstrated multiple ulcerative lesions from which herpes simplex virus type 2 was Isolated. (Reproduced with permission from Monif *et al. Am J Obstet Gynecol* 1985; 152:1000)

(3) evidence of herpetic and/or viral placentitis, the induction of which antedates rupture of the fetal membranes, which is associated with documented disseminated herpetic infection of the newborn.

Without virological confirmation the baby described by Schaffer and Avery would have been attributed to the cytomegalovirus. South *et al.* reported a case of a premature neonate with microcephaly, intracranial calcifications, micro-ophthalmus and retinal dysplasia who had vesicular skin lesions from which HSV-2 was recovered. Fagnant and Monif, using three criteria,

(1) herpetic infection and altered organogenesis of inflammatory etiology that antedates dissolution of the fetal membranes,
(2) documented herpetic infection present at birth and within 24 hours of rupture of the fetal membranes, and
(3) evidence of viral herpetic placentitis, the induction of which antedates rupture of the membranes, identified 15 cases of congenital transplacental HSV.

In this series, disease manifesting after the shortest recognized incubation period for the induction of the disease in experimental animals did not necessarily preclude transplacental acquisition.

The Centers for Disease Control (CDC) conducted an 18-month hospital-based surveillance study in which 184 cases of neonatal HSV infection were analyzed. Only 22% of mothers had a history of genital HSV infection and only 9% had genital lesions at the time of delivery. Cesarean delivery initiated prior to membrane rupture failed to prevent infection in 15 cases. Their data confirm previous observations that most mothers of infected neonates have no history of genital HSV and are asymptomatic at delivery. They concluded that intrauterine infection was an important route of transmission which underscores the limitations of our current prevention strategy.

Neonatal infection

Neonatal infection is the consequence of delivery of a neonate through an infected birth canal. Neonatal involvement characteristically appears between the fourth and tenth day. The length of the incubation period is a partial function of the inoculating dose of virus.

The infants may eat poorly and become listless and irritable. Cutaneous herpetic vesicles may or may not develop. In the next few days, depending on the organs involved and the extent of infection, the neonates may exhibit fever or subnormal temperature, cough, increased respiratory distress, cyanosis, tachycardia, jaundice, vomiting, diarrhea, irritability, and convulsions. A hemorrhagic diathesis associated with thrombocytopenia or

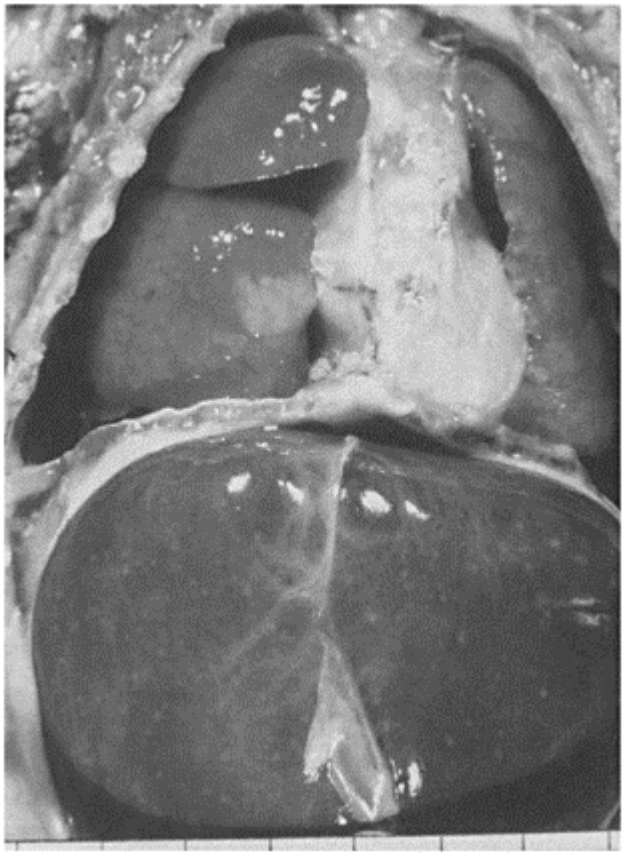

Figure 13.7 Miliary focal necrosis. Miliary involvement of liver and segmented involvement of the lungs of a term neonate who died of disseminated disease acquired at the time of parturition.

gastrointestinal bleeding from herpetic gastric ulcers or esophagitis may occur. The clinical course may terminate in irreversible vasomotor collapse or respiratory arrest.

At necropsy, affected infants exhibit miliary focal necrosis involving primarily the liver, lungs and adrenal glands (Figure 13.7). Microscopically, these lesions demonstrate focal, coagulative necrosis (Figure 13.8). At the margin of these areas of necrosis, the characteristic intranuclear inclusion bodies can be identified.

Thirty to forty percent of infected progeny will develop disease, which results in the death of 50–60% of those afflicted. Another 15–20% will develop permanent sequelae involving primarily the brain and eyes. Of the 326 cases of neonatal herpes summarized

by Nahmias *et al.*, 59% died. An additional 20% who survived had permanent ocular or central nervous system sequelae.

Probability of neonatal involvement

The simple presence of virus within the birth canal is not the sole determinant of disease. In the absence of any demonstrable lesion, sensitive virological techniques can demonstrate the presence of HSV in endocervical tissue of one to two percent of all gravid females. The incidence of isolation appears to increase in the third trimester. Asymptomatic occult shedding of HSV-2 can be demonstrated in 0.65–3.03% of cultures from pregnant women with a history of recurrent genital herpes. When serial specimens for culture are obtained, at least one episode of asymptomatic reactivation is detected in 2.3–14% of pregnant women with a history of genital herpes. As the number of antepartum culture specimens increases so does the incidence of culture-proven asymptomatic excretion. Among women with recurrent genital herpes antedating pregnancy, the mean number of recurrences per trimester increased from 0.01 to 1.26 to 1.63 in the first through third trimester. In a very real sense, one infant in 50–100 live births has been delivered through a birth canal harboring infectious virus, yet the incidence of disseminated herpetic infection of the newborn is extremely low, i.e. 1:20000 deliveries. The difference between these patients and gravida with overt herpetic vulvovaginitis is that in the former case, the quantity of virus present is limited to a few plaque-forming units, whereas in the latter the quantity of virus present is in the order of several logs of virus. While the quantity of virus present is a major factor in determining the probability of ensuing neonatal disease, almost equally important may be the duration of exposure to a given minimum quantum of virus, the genetic constitution of the infant and the presence of specific homologous neutralizing antibodies. The risk of infection for an infant born to a mother with primary herpetic vulvovaginitis is 30–45%. With active recurrent herpetic disease at the time of parturition, the risk of infection is estimated to be between five and eight percent.

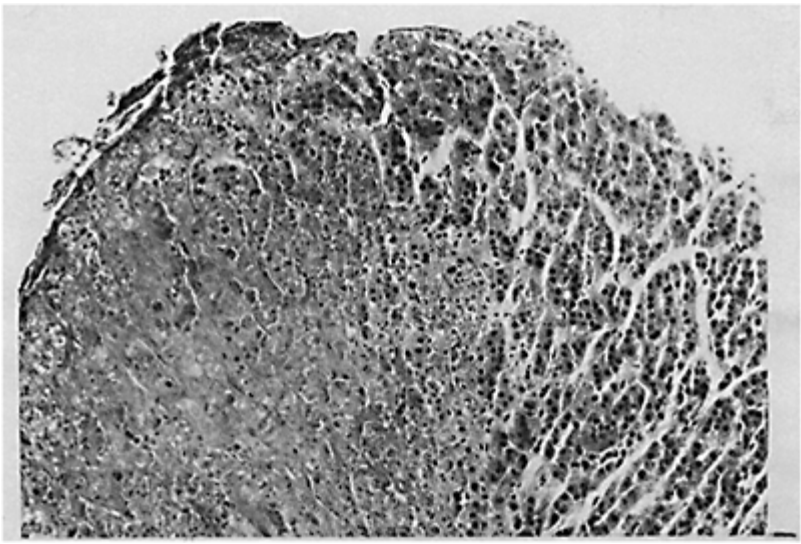

Figure 13.8 Photomicrograph of an adrenal gland exhibiting coagulative necrosis due to herpes simplex type 2 virus. (H&E, ×120)

The virtual disappearance of disseminated herpetic infection of the newborn from the neonatal nursery has focused on the question of resultant maternal morbidity. Once a disease is eradicated, the cost of its eradication is reevaluated. Cesarean section carries with it significant maternal morbidity and in rare instances mortality.

The rarity of neonatal disease has fostered the concept that cesarean section is unwarranted for recurrent herpetic vulvovaginitis. How completely maternal antibody will protect a neonate from infection during a recurrence is not well established. There have been several case reports describing neonatal infection in patients with high serum IgG antibody titers to HSV-2. Preexisting homologous and probably heterologous antibodies protect fully against congenital but not neonatal disease. The available data suggest that there is a risk to the neonate from any form of genital herpesvirus infection at term. It would be wise to continue delivering infected mothers with active disease by cesarean section.

Local neonatal infection may result from the use of fetal scalp electrode monitoring in which the portal of infection was the site of attachment of the scalp electrode used in internal fetal monitoring. If vesicular or vesiculopustular lesions develop at this site, it is imperative that immediate cytologic evaluation be carried out. If multinucleated giant cells with intranuclear inclusion bodies are identified, systemic chemotherapy should be instituted immediately

Nosocomial neonatal herpetic infection

The major emphasis has been placed on preventing acquisition of neonatal infection by avoiding delivery through an infected or potentially infected birth canal. The success of preventing **'baby and virus from ever meeting'** has overshadowed the fact that neonatal infection may be acquired independently of the events involved with parturition. Transmission of virus to the neonate may be mediated by individuals other than the mother and from sites other than the genital tract. The neonate, and particularly the premature neonate, is uniquely susceptible to the HSV. Postnatally, nosocomially acquired disease can be as lethal as that acquired by virtue of delivery through an infected birth canal. Oropharyngeal or cutaneous lesions can be an effective source of virus as primary herpetic vulvovaginitis. Most strains of HSV responsible for nosocomial neonatal disease are type 1 rather than type 2. One of the big problems in devising a management sequence is our current inability to document immunological competence on the part of the neonate. Should the infant contract herpetic infection after 15–20 days, the baby may become sick; however, permanent sequelae or mortality rarely ensue. Only when we can document T-cell competence for HSV in a given neonate, can the recommendations concerning the duration of relative isolation have validity. Given a woman with one or more active lesions at term, the policy is to institute appropriate isolation procedures (routine gown and glove isolation). Masks are added to the isolation regimen only if an oropharyngeal lesion is identified. While isolation precautions need to be implemented, bonding should be permitted. While separation of mother from her neonate up to one week of age can be implemented, concern must be given to the potential adverse effect on the establishment of a satisfactory mother-child relationship later in life. The mode of dissemination of the herpes virus is basically that of direct contact (hand-to-mouth type of dissemination). Care is taken to screen the father and other family contacts for the presence of oral lesions. The neonate born to a mother with prior primary infection during gestation will be isolated from other infants only if that child is at risk for congenital involvement. These children will be handled as potentially infected children and removed from the normal newborn nursery to a semi-isolated situation.

Nosocomial dissemination via breast milk

The question of breast-feeding in the immediate postpartum period has been complicated by the demonstration of neonatal HSV-1 infection. Serological studies demonstrated postnatal acquisition of infection for which breast milk was the vehicle of dissemination. The mother was found to have HSV-1 in her breast milk. She had no history of genital lesions. Viral cultures of cervix, vagina and throat were negative for HSV-1. Previously, Quinn and Lofberg reported the death of an eight-day-old breastfed neonate with disseminated HSV-2. The mother was subsequently found to have bilateral herpetic nipple lesions; however, concomitant cultures of the vulva and cervix also grew HSV-2. The presence of HSV in breast milk is not surprising. The cytomegalovirus which is also a herpesvirus is not an uncommon isolate from breast milk. The major question which needs to be resolved is whether the concomitant presence of specific secretary IgA

antibody can adequately function to render an infant relatively immune to infection. It is the opinion of the Committees on Fetus and Newborn and on Infectious Diseases of the American Academy of Pediatrics (1980) that breastfeeding can be attempted; however, careful attention to hygienic measures must be implemented to adequately protect the infant. The nipple should be examined to exclude the presence of herpetic lesions. In view of the occult transmission of the herpes simplex viruses in breast milk, it may be wise to individualize each case.

Management of active herpetic vulvovaginitis in pregnancy

When a pregnant patient presents with genital herpes, the physician must determine whether he is dealing with primary or recurrent herpetic infection. In most instances the solution does not require sophisticated laboratory backup, but can be made on clinical grounds: the number of lesions, their size, their distribution, the presence or absence of systemic symptomatology, etc. In primary herpetic infection, the immediate focus of management (beyond that of maternal pain and discomfort) is to determine whether or not an effective maternal viremia has occurred. Most people with primary infection to HSV-2 have preexisting cross-reacting antibodies to HSV-1 which will effectively abort type 2 viremia. A prior history of cold sores or the absence of systemic symptomatology argues against an effective viremia having been engendered. The critical focus of attention becomes the immediate antepartum period and the exclusion of recurrent infection. It the gravida gives a history of fever, pseudochills, myalgia, or arthralgia, these should be interpreted as indicative of an effective maternal viremia, and the possibility of congenital herpetic infection is raised. It was previously advocated that, approximately four to six weeks after primary infection, an amniocentesis should be performed and the amniotic fluid cultured for the virus. Based on observation derived from cases of congenital cytomegalovirus and rubella, it was postulated that recovery of herpes virus from amniotic fluid would be presumptive evidence of *in utero* infection and consequently, should overt disease be detected at the time of parturition, no advantage would accrue from cesarean section. This postulate may not be invariably correct for the HSV. To date, there has been a poor correlation between effective viremia as documented by systemic symptomatology and/or the absence of cross-reacting antibodies to the heterologous strain of HSV and congenital infection. Out of several hundred patients studied by amniocentesis, only three isolates have been achieved from amniotic fluid. In one instance, the neonate was free of any stigmata of disease at the time of parturition. In the other two cases, the infants were infected *in utero*. This observation, coupled with the rarity with which HSV functions teratogenically for the human fetus, has led to questioning the wisdom of resorting to such a procedure except within academic settings. Currently, culture of amniotic fluid for virus or analysis of amniotic fluid for viral antigens are not recommended unless the fluid is to be obtained for another diagnostic purpose or a high index of suspicion exists that *in utero* infection has occurred.

Given a patient with recurrent herpetic vulvovaginitis during pregnancy, no maternal viremia is engendered and, consequently, there is no potential for fetal involvement. Here management focuses on whether or not disease is present at the time of parturition. Given one or more maternal lesions at the time of parturition, the probability of neonatal

disseminated infection is in the order of 5–8%. The two most important variables which determine the probability of neonatal infection are:

(1) the amount of virus present; and
(2) the duration of labor.

Both variables must function in concert to achieve neonatal involvement with any degree of regularity.

In the presence of one or more lesions, it is our recommendation that cesarean section be performed. The cardinal point of therapy is that delivery must not occur through the birth canal harboring virus. In the absence of congenital involvement, cesarean section prior to the rupture of the fetal membranes is effective in circumventing neonatal infection. Once the fetal membranes have been ruptured, both HSV-1 and HSV-2 have the ability to ascend and infect the fetus *in utero*. With the advent of antiviral therapy of the newborn, the duration of rupture of membranes is not the important clinical factor, but the estimated time of delivery once the mother presents in labor.

Scott *et al.* have reported a small randomized, double-blind clinical trial in which women with clinically first-episode genital herpes during pregnancy received daily acyclovir treatment initiated in week 36 of gestation. They were able to demonstrate a reduced need for cesarean section. The ability of acyclovir, famciclovir, and valacyclovir to diminish viral shedding has brought into question the use of antiviral therapy for gravida with lesions in close proximity to parturition, but not fulfilling guidelines for cesarean section. The Centers for Disease Control and Prevention and Glaxo-Welcome have maintained a voluntary registry of women who have received acyclovir or valacyclovir during pregnancy (1-800-722-9292). Women who received acyclovir in the first trimester and whose birth outcomes were known had a 2.3% prevalence of birth defects as compared to a background rate of 3%. A theoretical concern is the development of obstructive uropathy in newborns, secondary to acyclovir crystals.

Virological monitoring during pregnancy

Whatever management scheme is to be developed for the prevention of neonatal herpetic disease will be predicated upon less than optimal scientific data. The future schema will probably be built around two basic tenets:

(1) the probability of fetal-neonatal involvement increases following primary herpetic vulvovaginitis in pregnancy;
(2) the probability of neonatal disease is greater when one or more lesions are present at the time of parturition.

Influence of primary herpetic vulvovaginitis on neonatal outcome

Brown *et al.* prospectively followed 29 patients who had acquired genital herpes during pregnancy. Fifteen patients had a primary episode of genital HSV-2 and 14 had a nonprimary first episode. Six of the 15 gravida with primary genital herpes but none of the 14 with nonprimary first episode infection had infants with serious perinatal morbidity. Four of the five infants whose mothers acquired primary HSV in the third

trimester had perinatal morbidity which included prematurity, intrauterine growth retardation, and neonatal infection with HSV-2. Perinatal complications occurred in one of the five infants whose mothers acquired primary HSV-2 during the first trimester as well as one of the five infants who had primary HSV-2 during the second trimester. Asymptomatic cervical shedding of HSV-2 was detected at 10.6% of weekly visits made after a primary first episode as compared to 0.5% of visits made after a nonprimary first episode.

One of the factors selected for the increased prevalence for neonatal involvement following primary herpes appears to be the occurrence of *in utero* hematogenous involvement. Fagnant and Monif have identified fifteen well documented cases of congenital involvement in which disease or its impact on organogenesis clearly antedated the rupture of the fetal membranes. When well-documented cases of congenital involvement as well as those of probable congenital acquisition were combined, they constituted approximately 5% of all the cases that had been reviewed.

Significance subclinical viral shedding

A second factor which influences the probability of an adverse fetal outcome is the greater incidence of clinically overt recurrent infection as well as asymptomatic shedding in gravida whose primary disease occurs during gestation. Brown, in another study, documented that asymptomatic secretion from the genital tract was more common in women whose first episode of genital herpes was acquired in pregnancy, 33%, than in women whose disease antedated pregnancy, 12.9% ($p<0.05\%$). Following primary infection there may be continued viral shedding in the absence of clinically discernible disease.

A third factor selecting for a higher probability of disease induction is the amount of virus present. In most cases of asymptomatic shedding the amount of virus present is low (less than one log). When one or more lesions are present, the quantity of virus recovered from such lesions is in the order of 4 or 5 logs of virus.

Fifty to seventy percent of neonates with HSV infection are born to mothers who do not have a history of peripartum genital herpes infection.

HIV-positive women have an increased tendency for genital shedding of virus, herpetic lesions persist longer, and may become chronic ulcerations.

Who and when to culture

Virological monitoring has proven to be both costly and noneffective. The correlation between asymptomatic viral shedding and ensuing neonatally acquired disease is poor. Unless a portal of infection is incidentally established, i.e. scalp electrode site, and in the absence of lesions in the periparturitional period, the probability of ensuing neonatal disease appears to be exceedingly low. Prior disease that antedates this gestation is not a sensitive predictor of ensuing fetal disease. Negative cultures probably do not preclude the possibility of subsequent neonatal involvement. Current policy is not to institute virological monitoring in gravida whose onset of disease antedated pregnancy or whose sexual consorts have had herpetic lesions. Similarly, current information does not support the value of culturing asymptomatic patients with a history of recurrent disease.

There is no justification for cesarean delivery in women with a history of HSV infection but no active disease during the last weeks of pregnancy. In the absence of lesions in the periparturitional period, the probability of neonatal disease appears to be exceedingly low. The presence of virus at parturition in a gravida whose disease antedates this gestation is not a sensitive predictor of ensuing fetal disease.

Negative cultures probably do not preclude the possibility of subsequent neonatal involvement. The reason for this is that type 1 disease which occurs in the neonate may be acquired from family contact and nursing personnel and not the consequence of delivery through an infected birth canal. To identify the 1–2% of gravida whose herpetic infection antedates gestation and who are excreting virus at the time of parturition requires that 200 to 500 cultures be obtained. If these women with low titers of virus are then allowed to deliver vaginally, estimated probability of neonatal involvement is significantly less than 1%.

Just as current monitoring policies have failed to totally preclude neonatal involvement, it must be understood that the new policies will fail to preclude sporadic occurrence of disease in the neonate. The difference between previous and currently advocated positions is that the latter are more rational and more cost effective. Failure of the current policies will occur because of

(1) asymptomatic primary herpetic infection during gestation and subsequent hematogenous dissemination to the fetus may occur;
(2) rupture of the fetal membranes introducing distinct potential for ascending infection;
(3) direct mechanical inoculation associated with the use of a scalp electrode in an asymptomatic shedder;
(4) distinguishing nosocomially acquired disease from parturitionally acquired disease may be difficult.

Primary infection during pregnancy

These individuals constitute a higher risk group than do gravida whose disease antedates gestation. The absence of episodes of symptomatic genital HSV infection throughout pregnancy does not eliminate the risk of asymptomatic shedding at delivery. There is limited data concerning prevention of disease in the fetus with maternal antiviral therapy. Acyclovir, famciclovir and valacyclovir can reduce viral shedding and shorten the duration of lesions. In theory, the reduction of the magnitude of the viremia and its duration should lessen the risk of transplacental viral dissemination in a nonimmune gravida.

If the fetus develops an abnormal biophysical profile, an amniotic fluid sample can be obtained for either culture or testing for virus-specific antigens using PCR or ligase chain reaction (LCR) technology.

Maternal herpetic genital tract disease antedating gestation or history of genital tract disease in sexual consort

If there are no recurrences during pregnancy and no lesions are present at the time of parturition, vaginal delivery has been advocated.

Presence of clinically overt disease at parturition

The presence of one or more lesions at parturition is a contraindication to vaginal delivery. Clearly when primary disease is present, there will be near unanimity on this point. With limited recurrent disease, even though the estimated risk may also be less than 5%, the ability to lower it to less than 1% mandates implementation of current protocol which uses cesarean section.

There is a continued need to identify gravida who have any risk factor which antedated gestation. Gravida with prior herpetic genital tract infection, herpes infection in consort, and women who are on immunosuppressant therapy should be prospectively identified to the neonatologists.

A unique situation arises when maternal genital HSV infection manifests in an immature, nonviable gestation in conjunction with documented rupture of the fetal membranes (ROM). What we would do after an informed consent is obtained is to put the patient on parenteral antiviral therapy and manage the patient as one would any other gravida with ROM and a previable fetus whose gestational age precluded reasonable lung maturity. The use of corticosteroids to accelerate pulmonary maturity needs to be carefully evaluated. Parenteral antiviral therapy is continued until termination of viral synthesis is documented. Thereafter, conversion to oral drug is implemented and therapy is continued until parturition. This approach is totally experimental.

Therapy in pregnancy

Approximately 1500 to 2000 newborns in the United States contact neonatal herpes each year. Infections occur in the perinatal period from contact with infected maternal secretions in the majority of cases. Mothers who do not know they are infected with genital herpes and shed the virus without lesions or symptoms give rise to most infected newborns. Alternative management of these women to prevent the transmission of this virus is being studied. The current management that relies on cesarean delivery has many disadvantages.

A viable alternative is antiviral therapy of the mother to prevent maternal symptomatic and subclinical viral shedding during the intrapartum period.

Other examples of prophylactic antiviral therapy have been shown to be safe and effective in reducing the spread of HIV from mother to newborn. In cases of disseminated HSV, herpes pneumonitis, herpes hepatitis, and herpes encephalitis, antiviral therapy using acyclovir has been life saving to mother and fetus. The use of antiviral medication in the last few weeks of pregnancy to suppress recurrent disease is being studied. Acyclovir is a class B medication as categorized by the FDA. The newer anti-herpetic drugs valacyclovir and famciclovir are also class B. Studies on acyclovir in pregnancy are the most complete. When acyclovir is given by the oral or intravenous route to the mother the drug crosses the placenta, is concentrated in amniotic fluid and breast milk and reaches therapeutic levels in the fetus. Starting in 1984, an acyclovir pregnancy registry has been compiled. The CDC published data in 1993 showing there was no increase in fetal problems in women who received acyclovir in the first trimester of their pregnancy. The registry continues to accumulate this information.

Scott *et al.* studied a small number of pregnant women to see if suppressive therapy started at 36 weeks gestation could decrease viral shedding and allow for a vaginal

delivery. This study is a start in the use of antiviral therapy to prevent cesarean sections and decrease viral shedding to prevent neonatal herpes.

Larger, more comprehensive studies on antiviral therapy in pregnancy will be soon reported. The newer recommendations to reduce the number of newborns infected with HSV will combine serological testing of all pregnant women for antibodies to HSV-1 and HSV-2 using a type specific glycoprotein gG based test and the use of antiviral therapy starting at 36 weeks in selected cases. Intervention is aimed primarily at preventing primary infection in those women at risk for HSV.

Prevention of sexual transmission

Abstinence is advised when prodromal symptoms develop or one or more lesions is identified. Antiviral therapy, by suppressing viral replication may result in decreased transmission of infection to sex partners in discordant couples. In theory, the use at the time of intercourse of Nonoxynol-9 and a condom may afford another layer of protection; however given the wide distribution of herpes during reactivation, these measures may not suffice.

In stable, established relationships, serological type-specific testing is advised. Often as not, transmission of infection has occurred.

Information and its sharing are the keys to prevention. A HSV-infected woman needs to know that HSV can be sexually transmitted, how to detect the earliest symptoms of disease, the availability of suppressive therapy, the ability to obtain type-specific testing of sexual partners, and the potential dangers to the newborn when disease is present at parturition.

Pregnant women who are not infected with HSV-2 should be advised to avoid intercourse during the third trimester with men who have had genital herpes. Pregnant women who are not infected with HSV-1 should be counseled to avoid cunnilingus with any partner with prior oral herpes and genital intercourse with a partner with genital HSV-1 infection.

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14
Human immunodeficiency viruses

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The acquired immunodeficiency syndrome (AIDS) viruses belong to a group of viruses known as retroviruses or backward viruses. The retroviruses are ribonucleic acid (RNA) viruses which require an enzyme called reverse transcriptase for successful replication. Characteristically, the retroviruses can be subdivided into two groups: oncogenic viruses or lentiviruses. The AIDS viruses are primarily a group of simian or monkey retroviruses.

These human T-cell lymphotrophic viruses (HTLV) are related but distinct. HTLV-I is the causative agent of T-cell leukemia-lymphoma (ATL). The variability of this group has been demonstrated by the fact that over 200 HTLV-I isolates have been obtained since the virus was discovered in sporadic cases of adult T-cell malignancies. There is some evidence to suggest that the HTLV can be transmitted by homosexual sex. HTLV-I infection positively correlates with the duration of homosexuality and the increasing number of sexual partners. Most of the HTLV-I isolates are closely related. The virus is endemic in the Caribbean, South and Central America, southeastern United States, Africa and southern Japan. Presently, HTLV-I is present in 1 to 4% of the general population and 5 to 15% of the high-risk groups in the Caribbean. Dual infection with human immunodeficiency virus-1 (HIV-1) and HTLV-I does occur. The presence of HTLV-I may lead to a more rapid progression of HIV infection to AIDS.

HTLV-II shares many features with HTLV-I, but has some genomic differences. It has been isolated from a few patients with hairy cell leukemia. HTLV-II, like the AIDS virus HIV, appears to have its origin in Africa. It has been found in about 100 people in Europe where it has been the cause of a disease identical to AIDS.

HIV-1, originally called HTLV I and II, is responsible for the vast majority of cases of AIDS. This virus causes the body to lose its natural immunodefense mechanisms against disease. The body then becomes more susceptible to a whole set of illnesses ranging from mild to life-threatening conditions. A second retrovirus, HIV-2, has been identified as a causative agent of AIDS. HIV-2 is endemic to West Africa. Infection and disease due to HIV-2 have been diagnosed in Brazil, Europe and North America. The modes of dissemination and prevalent pathways for infection and disease closely parallel HIV-1. Recently, analysis of HIV-2 has shown that this virus is more closely related to the simian viruses than to HIV-1.

Infection of a cell requires the virus to bind to a specific receptor site on cells. HIV-1 and HIV-2 preferentially infect brain cells, the infected macrophages (glial cells) and the cells of the monocyte/macrophage group. HIV attachment requires the binding of the GP-120 surface glycoprotein to a specific CD4 receptor site. Expression of the CD4 receptor site may require antigenic stimulation; i.e., HIV is capable of infecting B cells only if prior infection with EBB is present.

HIV-1 AND HIV-2

Human immunodeficiency viruses are composed of a single strand of RNA with three principal genes: GAG which is associated with viral internal protein production, PAL which is associated with the reverse transcriptase production, and EB which is associated with surface proteins. While these three genes are inherent to all of the retroviruses, the immunodeficiency virus is unique owing to the presence of five additional regulatory proteins which have been termed SOR, TAT, RART/TRS, 3′ORF and R. While the exact nature of the regulatory genes has not been totally worked out, preliminary data suggest that SOR governs reduced virus replication but facilitates cell-to-cell spread. TAT acts like a fast forward for virus replication. RART/TRS is essential for virus replication and controls subunit synthesis. 3′ORF is a negatory regulator which keeps virus in the latent form. The function of R has yet to be defined.

HIV-1 and HIV-2 cause a slow and progressive destruction of T-cells and, in selected cases, brain cells despite an immune response. How and why it is able to escape immune surveillance is being extensively studied. The virus has the capacity to change some of its antigenic initiators of the immune response as well as the ability to set up a latent infection.

HIV-2 is less aggressive than HIV-1, both in terms of transmissibility and pathogenicity. Both sexual and perinatal transmission rates of HIV-2 are lower than those of HIV-1. Although the disease produced by HIV-2 is indistinguishable from that induced by HIV-1, the progression of immune deficiency is slower.

Based on viral genetic sequences, HIV-1 and HIV-2 viruses have been classified into number of subtypes. HIV-1 subtype B is the predominant subtype in the United States.

Transmission

While HIV-1 can be isolated in low numbers from saliva, tears and other biological fluids, all current scientific research indicates that the only valid mechanism for dissemination involves intimate sexual activity involving the repeated exchange of genital body fluids, infusion of blood or blood products, and the sharing of needles to inject drugs into body tissue.

HIV infection is transmitted primarily by sexual contact; from mother to neonate during pregnancy, delivery, and breast-feeding. World-wide, over 70% of HIV infection is due to heterosexual transmission. There is a link between drug users and sexual activity which tends to accelerate the dissemination of AIDS into a larger community. The combination of drug abuse and multiple sexual encounters renders these individuals at double jeopardy for exposure toHIV-1.

Sexual transmission

The estimated probability of HIV being transmitted by a single sexual heterosexual contact is estimated to between 0.03% and 0.09%. The probability of transmission in an individual case is governed by viral subtype, host immunity and selected environmental factors.

High plasma viral load correlates with increased genital viral shedding. Plasma viral loads tend to be elevated in the acute phase of infection and during the phase of immune suppression. Enhanced detection of HIV in cervicovaginal lavage is often correlated with decreased CD4 counts and increased viral load. Genital ulcers, due to a variety of sexually transmitted diseases (STDs), appear to increase the risk of transmission as does unprotected intercourse during menses. Increased genital shedding of HIV has been demonstrated in the presence of ulcerative and nonulcerative STDs.

STDs, such as gonorrhea or chlamydia or trichomoniasis, have been identified as risk factors for HIV transmission. The presumed mechanism is the recruitment of CD4+target cells to the affected area. Inflammation associated with selected STDs is thought to lead to increased proinflammatory cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor (TNF) alpha) production which can up-regulate HIV replication.

Three modes of maternal/neonatal transmission appear to function: *in utero*, during labor and delivery, and postpartum, primarily due to breast-feeding. Prior to the introduction of intrapartum therapy, perinatal transmission rates of 14–25% were documented in industrialized nations and 25–40% in developing countries.

Only 15–23% of neonatal HIV cases are presumed to be due to *in utero* acquisition. The vast majority occur during parturition and the early postpartum period. The remaining cases result primarily from breast-feeding in the late postpartum period. The likelihood of perinatal transmission has been dramatically decreased by intrapartum antiretrovirus therapy. While mother-to-child transmission of HIV can occur at anytime during pregnancy, the majority of women do not transmit HIV to their newborn infants.

The principal determinant of probability of maternal HIV transmission appears to be the viral load. Pregnancy *per se* does not appear to accelerate the progression of HIV infection into AIDS. Increased rate of transmission correlates with low CD4 counts. In the European Collaborative Study, an inverse correlation was demonstrated between a CD4 count of less than 200 and increased risk of transmission. When the CD4 count was greater than 800, neonatal transmission still occurred. In general the CD4 cell count and p24 antigenemia tend to reflect viral load.

In industrial nations, blood transfusion is becoming a rarer means of infection acquisition. While the risk of a healthcare worker acquiring HIV infection from a contaminated needle-stick is approximately 3 per 1000, a much more significant risk resides with drug users who share needles. Most individuals who are infected through blood develop specific HIV antibodies within the first 2–3 months.

Dissemination of HIV-1 from female to male appears to be more difficult than dissemination from a seropositive male to his partner. The sexual male consort of an HIV-1 -positive woman has a two to ten-fold lower risk of acquiring infection with HIV than in the converse situation. The probability of acquiring infection with HIV is ten times greater during a homosexual encounter between two men than during sex between a man and a woman.

The susceptibility of the endocervix/uterus as a potential portal for infection has been illustrated by women recipients of contaminated semen. Where semen from an HIV-1-positive male donor was used for artificial insemination of eight women, four developed AIDS-related complex (ARC). Although the pregnant women contracted the disease, none of the children born to these women contracted infection *in utero*.

The dissemination of HIV through artificial insemination has led to the change of the American Fertility Society's guidelines. Potential semen donors now are required to give a detailed sexual history, and to be tested for a variety of STDs.

Lyophilized clotting factor concentrates, agents used to stop bleeding, are the principal vehicles for the induction of infection in individuals with hemophilia. Blood products potentially capable of transmitting HIV include lyophilized clotting factor concentrates, platelets and white blood cells.

Blood products which do not harbor HIV-1 and therefore cannot transmit the virus are immunoglobulin, albumin, plasma protein fraction and hepatitis B vaccine.

AIDS:THE DISEASE

Acquired immunodeficiency syndrome, known by the acronym AIDS, is a virus-induced disease. The AIDS-causing virus, human immunodeficiency virus or HIV-1, attacks and destroys selected vital cells in the human body's immune system and brain. The destruction of lymphatic cells leaves an individual vulnerable, that is, without his or her natural defenses to microorganisms which under normal circumstances would not produce disease in immunologically intact individuals. In time, these opportunistic pathogens kill their host. Dementia, seen in HIV-positive individuals, can occur independent of opportunistic pathogens, due to a direct virus-brain cell interaction.

There is no definitive test for the disease, AIDS. What we have are tests for infection with the HIV virus which is anticipated to progress to full-blown disease, AIDS. The diagnosis of AIDS is made on clinical grounds. The Centers for Disease Control's (CDC) initial definition was the presence of biopsy-proven Kaposi's sarcoma in individuals less than 60 years of age and/or *Pneumocystis carinii* pneumonia (PCP) or another opportunistic infection in an individual who has no obvious underlying cause for immunosuppression and is HIV-positive.

Pneumocystis carinii is a protozoan parasite which causes pneumonia in immunosuppressed patients. The one-celled organism is acquired from the environment. Patients have fever and shortness of breath. They may cough, but they rarely produce sputum. Chest X-rays usually show diffuse interstitial infiltrates, or evidence of lung involvement, but may also be normal. Diagnosis of PCP is established by histologic demonstration of the cysts in lung lavage fluid or lung biopsy tissue.

Kaposi's sarcoma is a malignant neoplasm, that is, a tumor of the skin and mucous membranes and may affect parenchymal or adjacent structural organs. The initial manifestation of Kaposi's sarcoma is usually a blue to brown skin lesion (Figure 14.1). Mucous membranes and the soft palate are commonly involved.

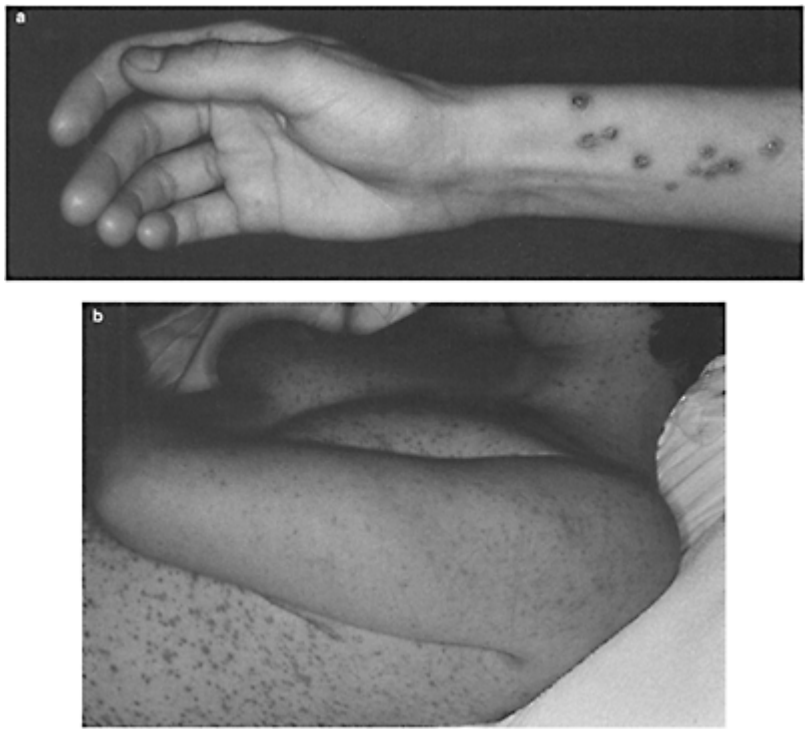

Figure 14.1 (a, b) Kaposi's sarcoma with extensive involvement of extremities and trunk

Any new skin lesion in a person at risk for AIDS should be biopsied as soon as possible. A diagnosis of Kaposi's sarcoma is established by identification of the typical histology in a biopsy specimen.

The initial CDC surveillance definition for AIDS became:

(1) the presence of a reliably diagnosed disease at least moderately predictive of cellular immune deficiency; and
(2) the absence of an underlying cause for the immune deficiency or of any defined cause for reduced resistance to the disease.

Subsequently, the AIDS definition was expanded to include the following diseases if accompanied by antibody to HIV-1: disseminated histoplasmosis, isosporia causing diarrhea for greater than one month, pulmonary candidiasis or lung infections due to certain fungi, nonHodgkin's lymphoma, and a special kind of pneumonia

Table 14.1 Revised CDC surveillance case definition for acquired immunodeficiency syndrome (AIDS)

Without laboratory evidence of HIV infection: If laboratory tests were not performed or gave inconclusive results, and in the absence of other causes of immune deficiency, any of the following diseases indicates AIDS:

1. Candidiasis of the esophagus, trachea, bronchi, or lungs
2. Cryptococcosis, extrapulmonary
3. Cryptosporidiosis with diarrhea persisting 1 month
4. Cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient>1 month of age
5. Herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient>1 month of age
6. Kaposi's sarcoma affecting a patient<60 years of age
7. Lymphoma of the brain (primary) affecting a patient<60 years of age
8. Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child<13 years of age
9. *Mycobacterium avium complex or M. kansasii* disease, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. *Pneumocystis carinii* pneumonia
11. Progressive multifocal leukoencephalopathy
12. Toxoplasmosis of the brain affecting a patient>1 month of age

With laboratory evidence for HIV infection: Regardless of the presence of other causes of immunodeficiency, in the presence of laboratory evidence for HIV infection, any of the following or preceding diseases indicates a diagnosis of AIDS:

1. Bacterial infections, multiple or recurrent (any combination of at least two within a 2-year period), of the following types affecting a child<13 years of age:
   Septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses), caused by *Haemophilus, Streptococcus (including Pneumococcus),* or other pyogenic bacteria
2. Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
3. HIV encephalopathy (also called HIV dementia, AIDS dementia, or subacute encephalitis due to HIV)
4. Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
5. Isosporiasis with diarrhea persisting>1 month

6. Kaposi's sarcoma at any age
7. Lymphoma of the brain (primary) at any age
8. Other non-Hodgkin lymphoma of B-cell or unknown immunologic phenotype and the following histologic types:
   Small noncleaved lymphoma (either Burkitt or non-Burkitt type)
   Immunoblastic sarcoma (equivalent to any of the following, although not necessarily all in combination: immunoblastic lymphoma, large-cell lymphoma, diffuse histiocytic lymphoma, diffuse undifferentiated lymphoma, or high-grade lymphoma)
   (Note: Lymphomas are not included here if they are of T-cell immunologic phenotype or their histologic type is not described or is described as "lymphocytic", "lymphoblastic", "small cleaved", or "plasmacytoid lymphocytic")
9. Any mycobacterial disease caused by mycobacteria other than *M. tuberculosis*, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. Disease caused by *M. tuberculosis*, extrapulmonary (involving at least one site outside the lungs, regardless of whether there is concurrent pulmonary involvement)
11. *Salmonella* (nontyphoid) septicemia, recurrent
12. HIV wasting syndrome (emaciation, "slim disease")

in children called pediatric chronic lymphoid interstitial pneumonia as well as dementia and a variety of wasting syndromes (Table 14.1) which can occur independent of significant immunological compromise.

The diagnosis of AIDS should be considered for any patient who presents with unusual pneumonia, meningitis, encephalitis, esophagitis, chronic enterocolitis, extensive mucocutaneous herpes, or a history of more than a 20-pound unintentional weight loss over a six-month period.

Abnormalities of immunologic function are often found in persons with AIDS. Lymphopenia, altered numbers of helper and suppressor lymphocytes, decreased *in vitro* lymphocytic proliferation in response to antigens and mitogens, anergy to delayed hypersensitivity skin testing, and increased levels of serum immunoglobulins and circulating immune complexes are commonly described. Although some of these tests may be within the normal range in any given AIDS patient, only rarely would a patient have normal responses to all tests.

The presence of one or more abnormal values may cause unnecessary anxiety in the patient who is HIV-1 positive, but not yet diagnosed as having AIDS. Isolated abnormalities have little predictive value for the presence or future occurrence of AIDS.

The diagnosis of AIDS rests upon evidence of malignancy and/or infection with one of the selected opportunistic pathogens (Table 14.2).

CD4+ T-lymphocyte categories

The three CD4+ T-lymphocyte categories are defined as follows:

Category 1: ≥500 cells/μl
Category 2:200–499 cells/μl
Category 3: <200 cells/μl

These categories correspond to $CD4^+$ T-lymphocyte counts per microliter of blood and guide clinical and therapeutic actions in the management of HIV-infected adolescents and adults. The revised HIV classification system also allows for the use of the percentage of $CD4^+$ T-cells.

HIV-infected persons should be classified based on existing guidelines for the medical management of HIV-infected persons.

Symptoms

Initial infection with HIV often does not cause any signs or symptoms.

Acute retroviral syndrome

When signs or symptom do occur, initial infection presents as an infectious mononucleosis-like illlness characterized by fever, malaise, lymphadenopathy and skin rash. If a sharp transient decline in the CD4+ T-cell count occurs at this time, opportunistic organisms may cause disease manifestation such as oral candidiasis. This syndrome frequently occurs in the first few weeks after HIV infection, before antibody tests become positive. Documentation that an illness is due to acute retroviral syndrome can be inferred by assaying for HIV plasma RNA. A positive test should be subsequently confimed by enzyme immunoassay and Western blot tests. Current guidelines suggest that persons with recently acquired HIV infection may benefit from antiretroviral drugs.

The signs and symptoms that AIDS victims eventually develop are primarily related to secondary pathogens. Disease results from the body's inability to abort infection or reactivation of dormant infection and its subsequent progression to disease. These symptoms are persistent and may include:

(1) extreme tiredness, sometimes combined with headache, dizziness, or light-headedness;
(2) continued fever or night sweats;
(3) weight loss of more than 20 pounds which is not due to dieting or increased physical activity;
(4) swollen glands in the neck, armpits or groin;
(5) purple or discolored growths on the skin or the mucous membranes (inside the mouth, anus or nasal passages);
(6) heavy, continual dry cough that is not from smoking or that has lasted too long to be a cold or flu;
(7) continuing bouts of diarrhea;
(8) thrush, a thick, whitish coating on the tongue or in the throat which may be accompanied by sore throat;
(9) unexplained bleeding from any body opening or from growths on the skin or mucous membranes; bruising more easily than usual; and
(10) progressive shortness of breath.

The incubation period

Seroconversion for antibodies to HIV usually occurs within three to six weeks following infection. In isolated instances the appearance of specific antibody does not appear until months later. The viral subtypes appear to be one of the variables influencing the time interval prior to antibody production. The onset of symptoms following infection with the HIV-1 virus (and presumably HIV-2) is thought to range from six months to ten or more years.

Disease progression

The immunologic hallmark of progressive HIV disease is the decline in the CD4+ lymphocyte count. Clinical manifestations are closely related to the CD4+ T-lymphocyte count which in otherwise healthy individuals declines at a rate of approximately 75/μl per year. In general, HIV-infected individuals do not manifest immune deficiency complications when the CD4+ lymphocyte count is 500/μl or above and rarely when the counts are above 350/μl. As counts decline below 350/μl, symptoms, such as oral or recurrent vaginal candidiasis, weight loss, herpes zoster, diarrhea, unexplained prolonged fevers, seborrheic dermatitis and the risk for other opportunistic infections increases. Bacterial infections such as pneumonia and listeriosis occur both early and late in the progression of induced immune deficiency. *Streptococcus pneumoniae* and *Hemophilus influenzae* are the most commonly identified pathogens. The risk of full blown disease and death occurs at CD4+ T-cell counts of 100–150/μl.

The median period to AIDS in seropositive cohorts in the industrialized world has been about 10 years.

CONSEQUENCES OF HIV INFECTION IN PREGNANCY

Maternal issues

If adjusted for stage of disease, pregancy *per se* does not appear to be an independent risk factor for disease progression. What pregnancy does is provide an opportunity for identification of HIV infection, education and early therapeutic intervention, over and above fetal/ newborn considerations.

Given the life-prolongation achievable with antiretroviral therapy and nonconsequential effects of pregnancy on survival more and more HIV-infected women will have the opportunity to be pregnant. In general HIV-positive women should receive the same therapy as if they were not pregnant; however, some antiviral therpy may need to be modified for fetal considerations. Efavirenz, a non-nucleoside reverse transcriptase should be substituted. Experimental use in pregnant monkeys resulted in anencephaly, anophthalmia and cleft palate being observered in 3 out of 13 study animals. Amprenavir is contraindicated owing to concerns that pregnant women may not be able to adequately metabolize propylene glycol. Hydroxyurea has been shown to be teratogenic in a number of animal species and similarly should be avoided. If one agent in a regimen is stopped, a

prudent decision is to replace it with an alternate drug. Continued updating of potential teratogenic effects of antiretrovirus drugs is available through the CDC web site.

HIV-infected gravida may decide to withhold new or on-going therapy in the first trimester owing to potential unidentified fetal risks. The potential risks of antiviral therapy to the fetus must be weighed against the risk of *in utero* transmission, progression of the immune deficiency and/or rebound in HIV titers. When restarted, all drugs in the regimen should be reinstituted simultaneously.

Since the vast majority of infants become infected in the intrapartum period, significant controversy has developed concerning the use of cesarean section delivery to reduce the potential for intrapartum dissemination. It is estimated that at least 40% and as high as 80% of perinatal HIV transmission occurs in the intrapartum period. Elective surgical delivery should preclude maternal-fetal transfusion as well as exposure to infected genital secretions. Abdominal delivery will not protect against transplacentally acquired infection.

There is no clear consensus on this issue, owing to the relative absence of prospective studies tightly focused on the matter. It is not uncommon for a physician to add the immunocompetence of the mother as a factor in determining whether surgery can be avoided. Pregnant women infected with HIV should have their viral load monitored. If, despite aggressive antiviral therapy, the viral load is greater than 1000 copies/ml, recognized leaders in this area such as Minkoff have argued for elective cesarean section at 38 weeks. In addition to antiretroviral therapy and possible cesarean section, vaginal cleansing with chlorhexidine has been used and may be of benefit for women who have had membranes ruptured for four hours or greater.

When alternate sources of sustenance are available, breast-feeding should be avoided.

Neonatal issues

The majority of infected children acquired HIV from their infected mothers, presumably due to transplacental infection or through blood and fluid exchanges in the birth process. Prior to screening of the blood supply, a few children developed HIV from blood transfusions. Currently, over 90% of pediatric HIV cases are believed to have been congenitally acquired. The fetus or infant becomes infected primarily by three mechanisms:

(1) infection of that portion of the placenta which has contact with maternal blood and is subsequently spread to the fetus (transplacental);
(2) secondary contamination with blood at time of birth; and/or
(3) ingestion of infected breast milk.

Probability of in utero *transmission*

Exactly what the probability is of an asymptomatic pregnant woman giving birth to an infected neonate is not known. Maternal-infant transmission rates vary widely in various regions of the world. In most areas, they were initially overestimated, biased towards investigating women with symptoms of HIV-1 disease, a factor known to lead to higher transmission rates. In the US 16% to 30% of maternal-fetal transmission rates have been recorded, with an incidence of 15% to 20% in Europe and 25% to 39% in Africa. Of

potential clinical relevance is the recent finding that rates of HIV-2 transmission may be much lower, possibly <5%.

St. Louis *et al.* demonstrated an inverse relationship between transmission and CD4+ percentage of total lymphocytes (transmission rates of 23%, 49%, 63%, and 77% for CD4+ cells of >30%, 20% to 29%, 10% to 19%, and <10%, respectively). When analysis was limited to values obtained during the third-trimester, Burns *et al.* found that women whose lowest antepartum CD4+ level was 20% were at a greater risk of transmitting HIV to their infant (42% risk vs. 18% in those with CD4+ levels >20%). The longer infection with HIV is present, the greater is the probability of *in utero* dissemination.

Determination of viral load defines disease activity, whereas CD4+ T-cell count defines the degree of immunocompromise present and the potential for opportunistic infections. Several methods are used to quantify HIV RNA. Thes include reverse transcription polymerase chain reaction (PCR), bDNA, and the nucleic acid sequencing-based amplification techniques. Ultrasensitive assays can detect as little as 50 copies/ml.

A variety of cofactors may be involved in facilitating vertical transmission of HIV. These include factors related to disease progression such as clinical status, CD4+ cell count, and p24 antigenemia, copresence of STDs, particularly when accompanied by chorioamnionitis, viral phenotype, titer and character of neutralizing antibodies, and genetic factors. Extreme prematurity is also associated with a higher rate of HIV transmission, with infants born at <34 weeks of gestational age 3 times more likely to acquire HIV. This has raised the possibility that a lack of transfer of specific maternal antibodies is involved.

The greatest probability of *in utero* transmission occurs when virus reappears in the blood and specific antibodies to the virus decline. Both advanced disease stage and immunologic deterioration are generally associated with increased levels of viremia; pregnant women with high viral load most likely represent a group with a particularly high potential for vertical transmission. Acute viremia associated with maternal seroconversion in the year prior to pregnancy or during breast-feeding also appears to be associated with higher rates of vertical transmission.

Once AIDS develops, the probability of transplacental transmission appears to increase. In one published study of 20 mothers with AIDS, who had previously given birth to infected infants, 13 transmitted the virus *in utero* to subsequent progeny. Even in cases of documented transplacental transmission, dissemination is not an all or nothing affair. At least two sets of twins have been born to mothers with AIDS in whom infections and disease developed in one newborn and not in the other.

HIV transmission rates are higher with vaginal delivery involving the use of vacuum extraction or episiotomy, but only in those hospitals where these procedures were not routine. A meta-analysis of eight studies did show a small but significant decrease in HIV transmission rates with cesarean section, though the magnitude of this difference did not provide a sufficient reason to recommend such a procedure in most cases.

The reason for this trend may reside with the status of the fetal membranes at the time of abdominal delivery. Landesmen *et al.* studied the impact of duration of rupture of the fetal membranes on the probability of ensuing neonatal infection. Among mothers with membranes that ruptured more than four hours before delivery, the rate of transmission of HIV-1 to the infants was 25%, as compared with 14% among mothers with membranes that ruptured four hours or less before delivery. In a multivariate analysis, the presence of

ruptured membranes for more than four hours nearly doubled the risk of transmission, regardless of the mode of delivery.

Adverse neonatal consequences

Disease which antedates a pregnancy or is manifested in pregnancy can have harmful effects on both the pregnant woman and unborn child. Of the 34 infants with AIDS or ARC reported by Minkoff *et al.*, approximately one out of three (11 of 34) were either low birthweight neonates and/or preterm births (11 of 34). In a majority of cases, siblings born before any affected offspring were significantly heavier. However, the majority of these infants were born to mothers who have a traditionally high incidence of low birthweight infants. Ryder *et al.* looked at the adverse neonatal/infant consequences of HIV-1 positivity compared to matched seronegative controls. Infants born to seropositive gravidas had:

(1) more frequent premature births;
(2) lower birthweights; and
(3) higher neonatal death rates at one year of age (21% vs. 3.8% had died).

The affected child's age at the onset of symptoms does not correlate with birthweight, mode of delivery or status of membranes at the onset of labor. The mode of delivery of a potentially HIV-1 infected neonate did not appear to adversely affect the development of pediatric illness. Operative cesarean section delivery did not guarantee neonatal well-being and is not warranted. If the neonate is infected *in utero*, the subsequent prognosis is poor. Sixty percent are dead within the first year of life. The principal clinical expression of pediatric AIDS or ARC is the development of pneumonia, enlarged lymph nodes, large liver, large spleen, or protracted diarrhea.

Not all infants who develop clinical AIDS are seropositive for HIV-1. Of 76 seronegative infants born to HIV seropositive gravidas reported by Ryder *et al.*, nine developed symptoms suggestive of AIDS despite continued seronegativity.

Postnatal transmission through breast milk

Breast-feeding is a clear risk factor. Fourteen percent of mothers who acquired HIV at or just prior to delivery infected their infants, whereas mothers infected post-delivery had a 29% (7–22%) transmission rate through breast-feeding. It is recommended that breast-feeding by infected mothers be discouraged in the US, although in underdeveloped countries the benefits of breast-feeding appear to outweigh the risk of virtual transmission. In the Third World countries, the decision as to whether or not an HIV-positive mother should breastfeed her newborn may be influenced by the availability of an alternative protein source for the infant.

PRENATAL SCREENING FOR HIV

To protect the unborn/unconceived child, the Centers for Disease Control initially recommended that antibody testing be used to help identify HIV-positive women and to encourage them to defer childbearing for the foreseeable future.

The potential of congenitally acquired disease is greatest for babies born to mothers with one or more of the following characteristics:

(1) women who have HIV infection;
(2) women who have previously delivered a baby with AIDS or ARC;
(3) women who have used drugs intravenously for nonmedical purposes since 1978 or whose sexual partners have done so in this time period;
(4) residents since 1978 of countries where heterosexual transmission is thought to play a major role, e.g., Haiti and central Africa;
(5) women who are or who have been sexual partners of intravenous drug abusers, bisexual men, men with hemophilia, men who were born in countries where heterosexual transmission is thought to play a major role in transmission of infection, or men who otherwise have evidence of HIV infection; and
(6) women who engage in prostitution.

The majority of congenitally infected infants are currently born to asymptomatic mothers, approximately one-third of whom have no immediately identifiable risk factors. Selective testing will not safeguard the workplace or significantly impact on the incidence of HIV-1 infection in pregnant women. What it may do is introduce a false sense of security which may increase the possibility of nosocomial infection among healthcare providers.

Even if cost-benefit was discarded as an argument against the implementation of compulsory screening, whatever advantages might be derived from this kind of program will be negated by three factors which are destined to rewrite current AIDS avoidance strategy:

(1) seronegativity does not preclude HIV infection;
(2) HIV-2 is being introduced into the United States and will spread in an insidious manner over the next two decades; and
(3) HTLV-I infection is increasing.

The public health problems created by HIV-1 will be compounded by the continued spread of HIV-2. HIV-2 is endemic to West Africa. The virus has recently been demonstrated to be in Europe, North America and Brazil. Cortes *et al.* have demonstrated that HIV-1 and HIV-2 dual infection does occur. The modes of dissemination of HIV-2 appear to be identical to those functioning for HIV-1. It is reasonable to assume that a pattern of penetration comparable to HIV-1 will materialize.

CDC RECOMMENDATIONS FOR HIV-2 TESTING

Because epidemiologic data indicate that the prevalence of HIV-2 in the United States is low, CDC does not currently recommend routine testing for HIV-2 at US HIV counseling and test sites or in settings other than blood centers. However, when HIV testing is to be performed, tests for antibodies to both HIV-1 and HIV-2 should be obtained when demographic or behavioral information suggests that HIV-2 infection might be present.

Another retrovirus, HTLV-I (human T-cell lymphotrophic virus type 1) which has been closely associated with leukemia, is presently evident in 1–4% of the general population in the Caribbean and 5–15% among high-risk groups for HIV-1. Dual infection with HIV-1 and HTLV-I does occur. It is distinct from the dual infection with HIV-1 and HIV-2. The presence of HTLV-I appears to accelerate progression of HIV infection to AIDS in addition to its own morbidity and mortality. The risk of HTLV-I infection from transfused blood products that have been screened for antibodies to HIV-1 is nearly ten-fold higher than the risk of HIV-1 infection.

Voluntary prenatal testing is needed, not for HIV infection identification, but as a vehicle to educate and alter risk-enhancing behavior to ALL the retroviruses. The CYA for healthcare professionals is not testing, but rather the aggressive implementation of universal precautions. Our current proposals for prenatal screening are time limited and do not adequately address the complexity in which the retroviruses and society interface.

Rather than advocating selective HIV testing in moderate and high prevalence areas, we should be moving towards a policy of education and offering of voluntary testing to all pregnant women. To impact on the dissemination of infection, every healthcare opportunity must be utilized to arm our patients with information by which they can make critical life decisions. For the majority of women, pregnancy is a recurring educational event.

USE OF ZIDOVUDINE TO REDUCE PERINATAL TRANSMISSION

In 1994, the Centers for Disease Control issued its recommendations for the use of zidovudine (ZDV) to reduce perinatal transmission (Table 14.2). The decision to do so was prompted by the ACTG Protocol 076ZDV study which indicated that ZDV would likely reduce the risk for perinatal transmission by about two-thirds. The following material is from their subsequent recommendations.

Clinical situation (CDC)

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/μl who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Discussion

The results of ACTG Protocol 076 are directly applicable only to women who meet the entry criteria for the study. The data from that study indicate that the complete ACTG Protocol 076 ZDV regimen will likely reduce the risk for perinatal transmission by about two-thirds.

Although ZDV was successful in reducing perinatal transmission, the study regimen did not completely prevent it. The possible reasons for transmission to these infected infants are being evaluated but have not yet been identified. Several case reports also have described perinatal transmission despite the initiation of ZDV therapy during pregnancy.

Although long-term toxicity to infants is unknown, this risk must be weighed against the decreased risk for transmission of an infection associated with substantial risk of death.

Recommendation

The healthcare provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category. This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known. The decision about this regimen should be made by the woman after discussion with her healthcare provider.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Discussion

This patient population has clinical characteristics similar to those of women enrolled in ACTG Protocol 076; the major difference is gestational age at which ZDV therapy would begin. Therefore, the ZDV regimen for these women would differ from the ACTG Protocol 076 regimen only in duration of antenatal therapy. As much as 50–70% of perinatal transmission may occur close to or during delivery. Therefore, the ACTG Protocol 076 ZDV regimen may have some benefit when initiated at>34 weeks of gestation, although the intervention is likely to decrease in effectiveness as the duration of antenatal ZDV administration is reduced.

A study evaluating the effect of ZDV on quantitative p24 antigen levels indicates that maximal effect is observed after 8–16 weeks of therapy. A shorter duration of ZDV therapy may thus be associated with an effect on maternal viral load that is less than can be anticipated when ZDV is initiated before 34 weeks of gestation. Both potential risks and benefits for the woman and her infant may decrease the closer to delivery that the ZDV regimen is initiated.

Recommendation

The healthcare provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200/µl who are at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Discussion

Women in this group meet the current standard of care for ZDV treatment of HIV infection for their own benefit; therefore, administration of ZDV during pregnancy for these women provides direct benefit to them as well as potential benefit to their infants. The risk for HIV transmission to the infants of HIV-infected pregnant women with low CD4+ T-lymphocytes or percent of total lymphocytes ranges from 22% to 60%.Viral load has been shown to increase as CD4+ T-lymphocyte count decreases; thus, baseline viral loads can be expected to be high among the women in this group.

Although viral replication and resultant capacity for mutations in this group are high, preexisting ZDV-resistant viral strains are unlikely to be present because these women have had little or no exposure to ZDV. Therefore, ZDV therapy can be expected to result in an acute reduction in maternal viral load analogous to that observed in women who have CD4+ T-lymphocyte counts ≥200/µl. Additionally, the mother's CD4+ T-lymphocyte count would not be expected to affect ZDV levels or toxicity in the infant after administration of ZDV during labor and the first 6 weeks of life. Hence, maternal CD4+ T-lymphocyte count should not affect the potential utility of neonatal levels of systemic ZDV for reducing intrapartum transmission.

Recommendations

The healthcare provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit. The intrapartum and neonatal components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Discussion

Women who have received extensive prior ZDV therapy may be infected with viral strains with reduced susceptibility to ZDV. These resistant strains of HIV can be transmitted from mother to fetus; however, the frequency with which such transmission occurs is unknown.

Resistant virus appears to emerge more quickly if therapy is initiated at later stages of HIV disease. The appearance of mutations associated with ZDV resistance follows a temporal pattern, and the level of *in vitro* resistance is proportional to the number of mutations in the reverse transcriptase-coding region of HIV. Phenotypically and genotypically diverse HIV populations can coexist in patients who are receiving ZDV therapy.

In one study, ZDV-resistant strains appeared earlier during ZDV therapy in patients with advanced HIV disease than in patients whose ZDV therapy was initiated at an early stage of the disease. After 12 months of ZDV therapy, viral isolates from 89% of patients with late-stage disease and 31 % of those with early-stage disease were resistant. However, isolates from only 33% of late-stage patients demonstrate high-level resistance (defined as a 100-fold decrease in susceptibility. Resistant virus also was more likely to be isolated from patients who had low CD4+ T-lymphocyte counts when therapy was initiated: 1-year estimated rates of resistance in patients with baseline CD4+ T-lymphocyte counts of >400, 100–400, and <100 cells/μl were 27%, 41%, and 89%, respectively. In patients with advanced disease, high-level resistance develops after 6–18 months of therapy. However, in patients with early-stage disease, high-level resistance appears to be delayed until after 24 months of therapy. Therefore, ZDV-resistant strains are likely to be more common in women with advanced disease who have received prolonged therapy.

ZDV-resistant viral strains also may be more common in persons receiving alternative antiretroviral agents because their disease progressed while they were receiving ZDV therapy. There is controversy regarding the association of clinical disease progression during ZDV therapy with the development of ZDV resistance and regarding whether resistance persists when therapy is changed to an alternative antiretroviral agent. Some studies involving small numbers of children have indicated that *in vitro* susceptibility to ZDV is correlated with clinical outcome, suggesting that ZDV-resistant isolates are associated with diminished efficacy of ZDV and more rapid clinical progression.

However, at least one study indicated that disease progression may be associated more closely with the development of syncytia-inducing viral phenotype than with resistance to ZDV. Change to alternative antiretroviral therapy has been associated with reversal of ZDV resistance in some studies, but resistance has been reported to persist for considerable periods of time after discontinuation of ZDV. The prevalence of ZDV-resistant viral strains in women who are receiving alternative antiretroviral agents because of disease progression has not been defined.

The capability of ZDV to reduce HIV transmission may be decreased for mothers in whom ZDV-resistant strains predominate, particularly if the strains have highlevel resistance; however, this assumption is not yet supported by data. Further clinical trials to evaluate alternative approaches for such women are needed.

Recommendation

Because data are insufficient to extrapolate the potential efficacy of the ACTG Protocol 076 regimen for this population of women, the healthcare provider should consider recommending the ACTG Protocol 076 regimen on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed

include her clinical and immunologic stability on ZDV therapy, the likelihood that she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g. lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The healthcare provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Discussion

Data from studies in humans are insufficient to evaluate the potential effectiveness of ZDV in this situation. Because the mother's exposure to ZDV would be brief, such therapy can be expected to have no effect on the level of maternal virus in blood or genital secretions. However, because of the intravenous loading dose and continuous infusion of ZDV during labor, the infant will be born with circulating levels of ZDV similar to those of infants whose mothers have received antenatal as well as intrapartum ZDV. ZDV may have some utility for this group of patients regardless of whether the pregnancy is at term or preterm because the presence of systemic levels of ZDV in the infant before or shortly after HIV exposure through contact with the mother's blood and genital secretions during delivery may help prevent intrapartum transmission.

The intravenous route was chosen for drug dosing during labor in ACTG Protocol 076 because continuous intravenous infusion of drug after an initial loading dose results in predictable levels of ZDV in the mother. Under optimal circumstances, these maternal levels provide a substantial fetal blood level during birth, when the infant is presumed to be exposed extensively to HIV through contact with the mother's blood and genital secretions. Because gastric emptying is delayed during labor, the absorption of orally administered drugs is unpredictable. Therefore, oral administration of ZDV during labor might produce widely variable systemic levels in the mother and infant. Oral ZDV administered intrapartum cannot be assumed to be equivalent to the intravenous intrapartum ZDV component used in ACTG Protocol 076. Further studies are needed to characterize the pharmacokinetics of oral ZDV during labor.

Intrapartum ZDV cannot prevent the substantial number of infections that occur before labor. Therefore, ZDV administered only during labor and to the newborn may not be effective.

Because the mother would receive ZDV only during labor, her risk for developing resistant virus or ZDV toxicity would be minimal. The primary risk is that associated with an intravenous catheter. The risk to the infant would be limited to the potential toxicity associated with transfer of drug from the maternal intrapartum infusion and with 6 weeks of oral ZDV therapy, without *in utero* exposure to the drug. The effect of neonatal ZDV treatment in ameliorating disease progression in infected infants is unknown. Clinical trials should be designed to address the efficacy of antiretroviral therapy in this situation.

Recommendation

For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the healthcare provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

PARTURITIONAL MANAGEMENT OF PROGENY OF HIV-POSITIVE GRAVIDA

The elective use of invasive procedures which may result in a maternal-fetal blood interface such as the use of scalp electrodes should be avoided. Blood and body fluids from pregnant women with one or more possible risk characteristics should be treated as if they harbored the virus. Great care should be exercised in avoiding exposure of the baby and others to blood and body fluids:

(1) healthcare providers should not handle newborns with bare hands until all secretory matter has been washed off;
(2) strict precautions similar to those employed for hepatitis B virus should be employed; and
(3) breast-feeding should be discouraged. Separation of the mother and infant postpartum does not appear warranted.

The precautions used in HIV-positive pregnant women are the same as those used for gravida who have serological evidence of hepatitis virus infection.

ANTE-, INTRA-, AND POSTPARTUM MANAGEMENT

The new therapeutic options have made AIDS a chronic disease. Voluntary HIV testing done early in pregnancy is identifying many gravida with early infection. Initial management begun in pregnancy can have long-term consequences for better mother and baby outcomes.

Management of the HIV-positive gravida involves more than antiretroviral therapy. Critical to management of such a patient is the quality of patient counseling for antepartum treatment, intrapartum, and postpartum treatment.

Preconceptional counseling

HIV positive women considering pregnancy can be divided in three main groups:

(1) HIV+ woman with HIV+ man;
(2) Discordant couple HIV+ woman and HIV− man;

(3) Discordant couple HIV− woman with HIV+ man.

HIV+ woman with HIV+ man

When both partners are HIV positive, vertical transmission rates depending on treatment and immune status can vary from 1% to 50%. In an untreated population with no formal care, vertical transmission can be as high as 33%. If breast-feeding is added to this rate, it will increase by 20% taking the vertical transmission rate up to 50%. If viral loads are less than 1000 copies/ml (HIV-1 RNA), the vertical transmission rate has been reported to be as low as 1 %, but still not zero percent.

Patients who are not pregnant but on HAART (highly active antiretroviral treatment) therapy should not be advised to stop or change therapy unless the combination

Table 14.2 CDC situations and recommendations for use of zidovudine to reduce perinatal HIV transmission (1994)

*Note:These recommendations do not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question.

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/µl who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation: The healthcare provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category.This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Recommendation: The healthcare provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-Lymphocyte counts <200/µl who aro at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation: The healthcare provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit. The intrapartum and neonatal components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Recommendation: Because data are insufficient to extrapolate the potential efficacy of the ACTG

Protocol 076 regimen for this population of women,the healthcare provider should consider recommending the ACTG Protocol 076 regimen on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed include her clinical and immunologic stability on ZDV therapy, the likelihood she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g., lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The healthcare provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Recommendation: For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the healthcare provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

VI. Infants who are born to HIV-infected women who have received no intrapartum ZDV therapy.

Recommendation: If the clinical situation permits and if ZDV therapy can be initiated within 24 hours of birth,the healthcare provider should offer the ACTG Protocol 076 postpartum component of 6 weeks of neonatal ZDV therapy for the infant in the context of a risk-benefit discussion with the mother. Data from animal prophylaxis studies indicate that, if ZDV is administered, therapy should be initiated as soon as possible (within hours) after delivery. If therapy cannot begin until the infant is>24 hours of age and the mother did not receive therapy during labor, no data support offering therapy to the infant.

includes (Sustiva®) due to teratogenic potential of anencephaly. It is important that the coordination of any change be done as a team with the patient's HIV primary provider. Patients may have history of positive drug resistance studies (phenosense tests) or are drug intolerant or have shown failure to the treatment previously.

Discordant couple HIV+ woman and HIV− man

Having a HIV positive woman and a negative partner, the first big decision comes when the couple wishes for a pregnancy. This decision to do so or not to do so resides with the individuals involved. The physician should be informative, but neutral. If the male partner is negative, then the option for safely advised pregnancy should be discussed and explained clearly: patients take their basal body temperature, and when raised have their partner take his ejaculate and dispense it in the vagina via a syringe (assistance of a physician helps ensure better method) at the time of ovulation. This method prevents mucosal contact and the male partner is not at risk. This method can be done inexpensively with the use of disposable dixie cups and a turkey baster and a thermometer. The author has had patients achieve pregnancies with this technique.

Discordant couple HIV− woman with HIV+ man

When the woman is seronegative and the male partner is HIV positive, this situation presents a more difficult scenario. Two centers have used a method of sperm washings and *in vitro* fertilization (IVF). Financial and legal concerns may limit this approach.

Postconceptional counseling

Women presenting after having been diagnosed HIV positive are usually treatment naive patients and anxious. Supportive, psychologic, social, and medical care needs to be coordinated. Patients tend to be in a state of shock/denial (5 steps in crisis description) when asked what being HIV positive means to them the usual reply being, "it means I die." The patient should be given information on vertical transmission (Table 14.3) and the chronic nature of long-term actual treatment options.

The two big questions almost always asked by patients are:

Will being pregnant make the course of HIV in me worsen? The answer is NO. Early in the endemic, the only pregnant women being tested were very ill and this was felt to be the case. Cohort studies showed the pregnancy does not worsen the progression of HIV.

How does the HIV positivity of a newborn affect the pregnancy? The baby will be born with a positive blood test (detected by enzyme-linked immunogorbent assay (ELISA) Western blot) due to passive transmission of antibodies. Approximately 6 weeks postpartum, 66% of infants without treatment will be seronegative. It should be noted that with treatment, subsequent transmission can be as low as less than 1%.

Table 14.3 Relationship of antiretroviral treatment to vertical transmission

Antiretroviral treatment regimen	*Percentage of vertical transmission*
076 study AZT	8.3%
C/S+AZT	2%
HAART	Less than 1%
Bangkok oral AZT	9.4%
Uganda Nevirapine	13.3%
Nothing	33%
Nothing+Breast-feeding	50%

AZT, azidothymidine (zidovudine); C/S, Cesarean section; HAART, highly active antiretroviral treatment

Special considerations for treatment

It should be noted that some patients may choose to wait until after the first trimester to start therapy. Certain antiretroviral drugs should be avoided in pregnancy. Efavirenza

(Sustiva®) should not be used due to reports of anencephaly. Hydroxyurea is teratogenic and should not be used in first trimester.

There have been reports of lactic acidosis and hepatic steatosis in woman patients treated with nucleosides. Three maternal deaths have been reported due to lactic acidosis.

It should be noted that in countries where the AZT treatment option of the 076 study is not available, two alternatives have shown decreased transmission.

The Uganda study with nevirapine in labor found a 13.3% vertical transmission at 14 weeks. The Bangkok data with oral AZT had 9.4% transmission rate (Table 14.3).

Initial laboratory evaluation

(1) All patients that are newly diagnosed must have a repeat ELISA and Western blot done. In any large health system, mistakes occur. It is worth verifying the best test to rule out sample mix up. Some patients may have equivocal tests and actually be false positives.
(2) Patients should have baseline renal, liver function tests, RRR, Hepatitis B and C, complete blood counts and platelets. When indicated CXR and TB screening test.
(3) Baseline T-cell subset studies, and HIV and viral load studies.
(4) Certain experts recommend sensitivity testing either phenosenses or genotype in all positive HIV pregnant women. If the viral load is less than 50 to not detectable, this test cannot be done. Sensitivity testing is certainly important in nontreatment naive patients with especially high viral loads, or with evidence of resistance or failure of treatment. Mostly it is important when the main issue is to avoid the vertical transmission and disastrous outcomes for any newborn that may result positive for HIV transmission.
(5) Viral loads+CD4 counts should be monitored every three months and drawn at the time of delivery.

Treatment consultation and options

Indications for treatment of the asymptomatic patient when not pregnant are CD4 counts less 350/mm^3 and viral load (HIV-1 RNA) greater than 55000 copies/ml. These patterns will dramatically change during pregnancy; treatment should be offered if the level of HIV-1 RNA is more than 1000 copies/ml, rather than being above 55000 copies/ml.

With the advent of combination therapy, the use of single agent AZT would not be the standard in the nonpregnant state. Decreased vertical transmission with HAART therapy following decreasing viral loads has revealed a level of less than 1% over 100 patients in a cohort private patient population in Houston, Texas using Combivir® and Viracept® combined therapy. However, treatment options with combination therapy can be quite complicated.

INTERRELATIONSHIPS OF HIV INFECTION WITH OTHER SEXUALLY TRANSMITTED DISEASES

HIV infection appears to be facilitated by STDs that cause genital ulcers. Such STDs include syphilis, herpes simplex virus, and chancroid.

Studies in Kenya suggest an extraordinary impact of STDs on HIV spread. According to Eckholm, in partners free of venereal disease, the chance of transmitting HIV from an infected female to a male in a single act of vaginal-penile intercourse is below 0.2%, but the risk jumps to 5–10% when the woman has an active genital ulcer.

The immunosuppression produced by HIV infection can and does impact on other STDs. Cases have begun to be identified in which an altered response to standard therapy occurs in those STD diseases which require T-cell participation for resolution; prime examples are *Treponema pallidum* and herpes simplex viruses.

Several investigators have reported the development of neurological complications despite adequate penicillin therapy in HIV-positive patients infected with *Treponema pallidum*. These reports have suggested that penicillin alone is probably not adequate therapy to eradicate infection in the absence of vigorous host response. The immunologic response of patients appears to be important in controlling infection, even in the presence of adequate antibiotic therapy.

HIV-infected individuals have an increased incidence of anal and cervical cancer related to human papilloma virus types 16 and 18. Cervical intraepithelial neoplasia (CIN) is 4–5 times higher in HIV-seropositive women than in HIV-seronegative women.

DIAGNOSIS

There is no test to determine if a person has AIDS or will develop AIDS in the future. Tests have been developed for detecting antibodies to HIV-1. Presence of HIV-1 antibodies means only that a person has been exposed to the virus; it does not guarantee that the individual has or will develop AIDS.

Since there is no single diagnostic test for AIDS, diagnosis is based on evaluation of a variety of indicators including immune system function and presence of HIV-1 antibodies and AIDS-associated infections and diseases. The combination of HIV-1 antibodies in conjunction with demonstrable abnormalities of immunological function strongly favors the probability of disease in evolution.

HIV testing

Anonymous HIV-1 antibody testing is provided by many State Departments of Health for persons who wish to know if they have been exposed to the virus. Persons should receive counseling as to what the test results mean and what preventive actions they may take to minimize further exposure to the virus or potential transmission to others.

What must be stressed is that the test that detects antibodies to HIV-1 is not a diagnostic test for AIDS. Persons exposed to the HIV-1 virus may not develop AIDS.

What testing does do is to identify individuals capable of spreading the infection. All individuals infected with the HIV-1 virus—even those who remain completely symptom-free—probably will be infectious for their entire lives and be able to pass the virus on to others.

Antibodies to HIV-1 can be detected by several techniques. The principal techniques used are the enzyme-linked immunosorbent assay (ELISA) and the Western blot analysis. The ELISA test is used to identify the presumptive presence of antibodies against HIV-1 in a serum sample. The Western blot test permits documentation of antibodies to specific viral proteins and thus is a more specific test of serological reactivity.

A positive HIV-1 test by ELISA does not necessarily mean that an individual has been infected with the virus (Table 14.4). False-positive ELISA tests have been reported in association with the use of oral contraceptives and prior multiple births. Over 1000 ELISA-positive but Western blot-negative individuals have been serially followed. Not one of them has either developed antibodies to HIV-1 or developed signs or symptoms of disease. Confirmation requires the individual to have, concomitantly, a positive HIV-1 test by the Western blot method (Table 14.5). Even though rare cases of false-positive tests by both methods may exist, patients with antibodies to HIV-1 as determined by ELISA and Western blot must be considered infectious for purposes of transmission of the virus. Approximately 60% of individuals who test HIV-1 positive can be demonstrated to have the virus in their bloodstream. However, a positive antibody test is not diagnostic of disease. Not everyone with HIV-1 antibodies necessarily

Table 14.4 Disease entities associated with false-positive ELISA reactions

1.	Hematological malignancies (e.g., multiple myeloma)
2.	Acute DNA viral infections
3.	Alcoholic hepatitis
4.	Primary sclerosing cholangitis
5.	Autoimmune disease, i.e., rheumatoid arthritis, SLE

Table 14.5 Interpretation of Western blot results

Negative	No bands
Positive	Presence of P24, P31, and GP41 or GP160 bands
Indeterminate	Any bands which do not meet the criteria for positive

*Any individual with indeterminate test results must be retested.

develops AIDS-related complex (ARC) or AIDS; however, again, infected individuals may well remain infectious to others for life.

Congenital infection

Simply demonstrating placental infection does not necessarily imply fetal spread. Like rubella, placental infection can occur without subsequent engenderment of a secondary viremia. Diagnosis of HIV infection in children is confounded by the fact that maternal IgGs can cross the placenta and remain in the infant's circulation until approximately 18 months of age. Indeed by 10 months only one-half of infants have lost maternal anti-HIV antibody. Viral isolation, proviral amplification by PCR, and other technologies will provide the potential of therapy such that a commitment to treatment will be implemented pending documentation at time-points 3 months postpartum.

ACOG's position on HIV testing

Prior to July of 1996, the American College of Obstetricians and Gynecologists (ACOG) advocated that HIV testing be offered to pregnant women thought to be at high-risk. Because of the following three factors, this policy was changed:

(1) women of child-bearing age make up the fastest-growing population of new HIV infections in the United States;
(2) the rate of transmission of HIV from pregnant women to their newborns ranges from 25% to 28%;
(3) treatment of pregnant women during pregnancy and delivery and their newborns following delivery with zidovudine can reduce the rate of transmission by approximately two-thirds, according to the National Institutes of Health-sponsored AIDS Clinical Trial Group 076 study

ACOG currently recommends:

(1) that all pregnant women receive HIV education and counseling as part of their regular prenatal care; and that
(2) HIV testing be performed in all pregnant women with their consent.

Diagnosis of HIV-2 infection

Although considerable serologic cross-reaction occurs between HIV-1 and HIV-2, HIV-2 infection may not be diagnosed when screening is done exclusively with HIV-1 tests. From 60% to 91% of HIV-2-infected persons will test repeatedly reactive by HIV-1 whole-virus lysate enzyme immunoassay (EIA). Because HIV-2 infections are not always detected by HIV-1 antibody tests, antibody tests for HIV-2 have been developed. On April 25, 1990, the Food and Drug Administration (FDA) licensed an EIA test kit for detection of antibodies to HIV-2 in human serum or plasma. According to data provided to the FDA by the test manufacturers, HIV-2 antibodies are detected with>99% sensitivity by FDA-licensed HIV-1/HIV-2 EIAs and the FDA-licensed HIV-2 EIA. However, analogous to the diagnosis of HIV-1 infection, diagnosis of HIV-2 infection requires more specific supplemental tests, such as an HIV-2 Western blot. The diversity of protein bands, especially glycoprotein bands, is greater on the HIV-2 Western blot

tests than on HIV-1 Western blot tests. This variation occurs because the various HIV-2 Western blot tests use different strains of HIV-2 and because of the different methods by which HIV-2 antigens are prepared before separation by electrophoresis.

The following procedures have been recommended if testing for both HIV-1 and HIV-2 is performed by means of a combination HIV-1/ HIV-2 EIA. A repeatedly reactive specimen by HIV-1/HIV-2 EIA should be tested by HIV-1 Western blot (or another licensed HIV-1 supplemental test). A positive result by HIV-1 Western blot confirms the presence of antibodies to HIV, and testing for HIV-2 is recommended only if HIV-2 risk factors are present. If the HIV-1 Western blot result is negative or indeterminate, an HIV-2 EIA should be performed. If the HIV-2 EIA is positive, an HIV-2 supplemental test should be performed.

Indications for testing for HIV-2 infection

Persons at risk for HIV-2 infection include:

(1) sexual partners of a person from a country where HIV-2 is endemic (this category includes persons originally from such countries);
(2) sexual partners of a person known to be infected with HIV-2;
(3) persons who received a transfusion of blood or a nonsterile injection in a country where HIV-2 is endemic;
(4) persons who shared needles with a person from a country where HIV-2 is endemic or with a person known to be infected with HIV-2; and
(5) children of women who have risk factors for HIV-2 infection or who are known to be infected with HIV-2.

Additionally, testing for HIV-2 is indicated when there is clinical evidence for or suspicion of HIV disease (such as an AIDS-associated opportunistic infection) in the absence of a positive test for antibodies to HIV-1 and in cases in which the HIV-1 Western blot exhibits the unusual indeterminate pattern of GAG (p55, p24, or p17) plus POL (p66, p51, or p32) bands in the absence of ENV (gp160, gp120, or gp41) bands.

Table 14.6 Blood and body fluid precautions

(1) Blood and other specimens should be labeled prominently with a special warning,such as ‘Blood and Body Fluid Precautions’ along with the lab or specimen sheets. If the outside of the specimen container is visibly contaminated with blood or body fluids, it should be cleansed with household bleach and water (1:10 dilution). Clorox solution should be mixed and labeled for this purpose. All blood specimens should be placed in a second container, such as an impervious bag, for transport. The bag or container should be examined carefully for cracks or leaks.

(2) Pap smear slides should be labeled with a ‘Precaution’ label and placed in an empty Pap smear box that is also labeled. The box should then be placed in an impervious bag and taken to the lab. Remember to label the Pap requisition with ‘Blood and Body Fluid Precautions’.

(3) Blood spills, body fluids and secretions should be cleaned up promptly with a disinfectant solution of household bleach and water. Disposable gloves should be worn.

(4) Infectious waste hampers should be utilized for disposal of infectious waste (excluding sharps,

liquid body wastes, linen or instruments). Lined infectious waste hampers with infectious waste bags on the inside and clear autoclave bags on the outside are advocated.

(5) All contaminated linen should be placed in a water-soluble bag first and then into the nylon linen bag which is then taken to the area's respective dirty linen room.

(6) Examination tables should be wiped down using the Clorox solution in between patients when soiled with body secretions or fluids.

Antibody-negative HIV infection

There is something which we call the serological window in which the virus and its antigen constituents are present, but the IgG antibodies measured by both the ELISA and Western blot have not developed to detectable levels. There are sequential steps which permit for the documentation of a viral etiology:

(1) virus isolation;
(2) demonstration of specific viral antigens in blood or other biological fluids; and
(3) demonstration of special antiviral antibodies, first IgM and then IgG.

In HIV testing, we measure the last in this developmental series, namely, the development of specific antiviral IgG antibodies; hence there is a potential 3 to 6-month window in which an infected individual will not be identified by either the current ELISA or Western blot test. When antigen detection systems become the diagnostic standards, this problem will cease to exist.

How long is the serological window? If infection is acquired by blood transfusion or parenteral administration of blood products, the majority of individuals seroconvert within the first three months. If one looks at clinical illness associated with seroconversion, the great majority of these individuals manifest disease within the first eight weeks. When HIV-1 infection is acquired through the exchange of genital secretions, a more variable pattern of seroconversion occurs.

PREVENTION OF NOSOCOMIAL INFECTION

The Public Health Service (PHS) has outlined instructions for hospital workers who care for AIDS patients (Tables 14.6). The PHS recommendation is that people who care for AIDS patients should avoid direct contact of their skin and mucous membranes with blood and body fluids of patients with AIDS or AIDS-related disorders. Urine, feces, body secretions, and open wounds are likely to contain blood that harbors HIV. The PHS advocates that home care providers wear gloves when handling blood specimens, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials, and objects contaminated with these fluids. Unfortunately, the hysteria engendered by AIDS may kindle a renaissance of quackery. In the interim between the development of a vaccine to prevent HIV-1 infection and effective therapy to abort the progression of disease, the victims of AIDS also could become victims of dubious therapies which may mask some valid interim treatments.

To help the FDA identify such products, patients and health professionals are encouraged to submit examples of questionable AIDS products being marketed directly to the public or to health professionals to: FDA Health Fraud Staff, HFN-304, Center for Drugs and Biologics, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Data collected by the Centers for Disease Control have identified over 20 healthcare providers who appear to have contracted HIV-1 infection as a consequence of professional contact with patients with HIV-1 infection. The vast majority of these cases occurred after significant needlestick exposures to blood from patients infected with HIV-1. In a few cases, the individual acquiring HIV-1 infection did not sustain needlestick injuries, but rather had extensive contact with HIV-1-positive blood and had not observed routine recommended blood and body fluid precautions. These cases suggest that exposure of skin or mucous membranes to contaminated blood rarely may result in transmission of HIV and re-emphasize the need for healthcare workers to adhere rigorously to existing infection control recommendations for minimizing the risk of exposure to blood and body fluids of all patients.

Those who have chosen a healthcare profession need to clearly understand that their occupation, like those of the police and firefighters, has an inherent element of risk. Contact with sick people or their body fluids and tissues has always carried with it the possibility of illness resulting in death.

A healthcare provider is defined as any person, including students and trainees, whose activities involve contact with patients or with blood or other body fluids from patients in a healthcare setting. It is mandatory that all healthcare workers be educated about the following:

(1) virology of AIDS;
(2) modes of transmission;
(3) prevention of these infections;
(4) appropriate barrier precautions during procedures; and
(5) appropriate precautions when cleaning the environment during and after patient exposure.

CDC guidelines—universal precautions

Since medical history and examination cannot reliably identify all patients infected with HIV or other blood-borne pathogens, blood and body fluid precautions should be consistently used for all patients.

(1) All healthcare workers should routinely use appropriate barrier precautions to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. Gloves should be changed after contact with each patient.
(2) Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids. Hands should be washed immediately after gloves are removed.
(3) All healthcare workers should take precautions to prevent injuries caused by needles, scalpels, and other sharp instruments or devices during procedures; when cleaning used instruments; during disposal of used needles; and when handling sharp instruments after procedures.

(4) Although saliva has not been implicated in HIV transmission, to minimize the need for emergency mouth-to-mouth resuscitation, mouthpieces or other ventilation devices should be available for use in areas in which the need for resuscitation is predictable.
(5) healthcare workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care equipment until the condition resolves.
(6) Pregnant healthcare workers are not known to be at greater risk of contracting HIV infection than healthcare workers who are not pregnant.

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15
Human papilloma viruses

Stanley Gall, MD

Genital warts have been recognized for centuries and were described by ancient physicians as ‘condylomas’ or ‘figs.’ Despite this ancient association of condylomas and the female genital tract, the true etiology of genital warts has only recently been determined. Nonspecific material such as dirt and genital secretions was implicated in the development of ‘Venereal’ warts. In 1890 the histologic similarities between skin and genital warts were described. Skin warts were experimentally produced by inoculation of extracts of penile warts into nongenital epithelia. The viral etiology was demonstrated by the presence of viral particles using electron microscopy in 1949. Sexual transmission of genital warts was affirmed in 1954 although the concept of a common viral etiology for skin and genital warts had obscured the concept that genital warts were a sexually transmitted disease (STD). Sexual transmission of genital warts has been confirmed in several studies finding a high incidence in sexual contacts of those having the disease.

The spectrum of clinical disease that has been identified necessitates the use of the term human papillomavirus (HPV) infection rather than genital warts or condyloma acuminata. This spectrum has been extended to include entities such as subclinical HPV infection of the cervix, vagina, vulva, penis and scrotum, a relationship of HPV to intraepithelial neoplasia of the vulva, vagina, cervix, Bowen’s disease; and juvenile laryngeal papillomatosis. Because of the relationship to malignant disease and because HPV infection is among the most widespread of the STDs and difficult to treat, it has become a disease of potentially great concern.

There are four morphologic types of genital warts including condyloma acuminata which have the appearance of small cauliflowers; smooth papular warts which are dome shaped, flesh-covered 1–4 mm papules; keratotitic genital warts resembling a common wart or a seborrheic keratosis (thick horny layer); and flat warts which are flat to slightly raised flat-topped papules (Figure 15.1).

VIROLOGY

Genital warts are caused by specific types of HPV. HPV is classified with the papovavirus family (standing for papilloma, polyoma, simian kidney cell vacuolating virus). It is composed of double-stranded DNA with an average molecular weight of $5\times l0^5$ daltons. The viral DNA is present as a supercoiled covalently closed circle with an icosahedral capsid composed of one major structural protein. Other papilloma viruses include bovine papillomavirus (BPV) and Shope cottontail rabbit papillomavirus. Papillomaviruses are highly host and site specific and possess the ability to transform epithelial cells. HPV has not been convincingly cultured in tissue systems, probably

because productive viral infection requires a degree of keratinocyte differentiation which has not as yet been achieved.

HPV DNA has been molecularly cloned and more than 70 HPV types have been identified by DNA homologies. HPV types are correlated with anatomic sites and biologic behavior (Table 15.1). Genital warts are associated with HPV types 6, 11, 16, 18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 56, 58, 66 and 68 (Table 15.1). HPV types 6 and 11 are the most prevalent viral types in exophytic warts while HPV types 16, 18, 31, 33, 35, 45 and 56 are the types most associated with genital neoplasia (Figure 15.2).

The genomes of HPV as well as other papillomaviruses have been sequenced. The HPV genome does not need to

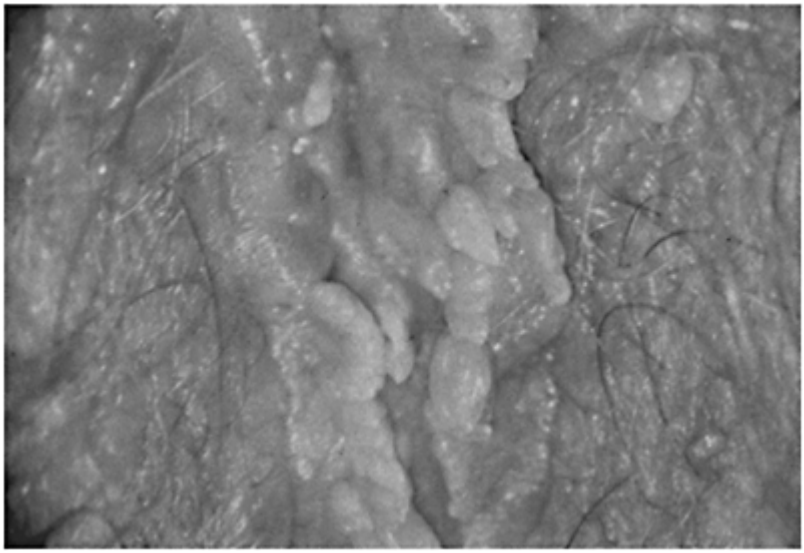

Figure 15.1 Vestibular condyloma presenting as pink, whitish or pigmented sessile projections with a lobulated surface

Table 15.1 Human papilloma viruses: type, disease and anatomic location, and malignant potential

Type	***Disease and/or anatomic site***	***Malignant potential***
1	Plantar and palmar warts	Benign
2	Common skin warts, occasionally associated with anogenital condylomata	Benign
3, 10, 28	Juvenile flat warts may be associated with epidermodysplasia verruciformis, genital infection and	Rarely malignant

	common warts	
4	Plantar and common skin warts	Benign
5, 8	Epidermodysplasia verruciformis associated with congenital or reduced cell-mediated immune deficiency	30% malignancy
6, 11	Anogenital condylomata acuminata flat condylomas, CIN I, II, juvenile and laryngeal papillomas	Usually benign
7	Common warts of meat and animal handlers	Benign
9, 12, 14, 15, 17, 19–25, 36, 40	Epidermodysplasia verruciformis	Several progress to malignancy
12, 17, 20, 16, 18, 31 33, 35, 39, 45 51, 52, 56, 58	CIN II, III, carcinoma *in situ* of genital tract, Bowenoid papulosis, Bowen's disease, laryngeal, esophageal and some bronchial carcinomas	Frequent progression to malignancy
13, 32	Oral focal epithelial hyperplasia	Possible progression to malignancy
26, 29	Cutaneous warts, immunodeficient patients	Unknown
30, 40	Laryngeal carcinoma	Malignant
34	Nongenital Bowen's disease	CIS
37	Keratoacanthoma	Benign
38	Epidermodysplasia verruciformis	Malignant
41	Condylomas, cutaneous flat warts	Benign
42, 43, 44	Genital warts	Benign

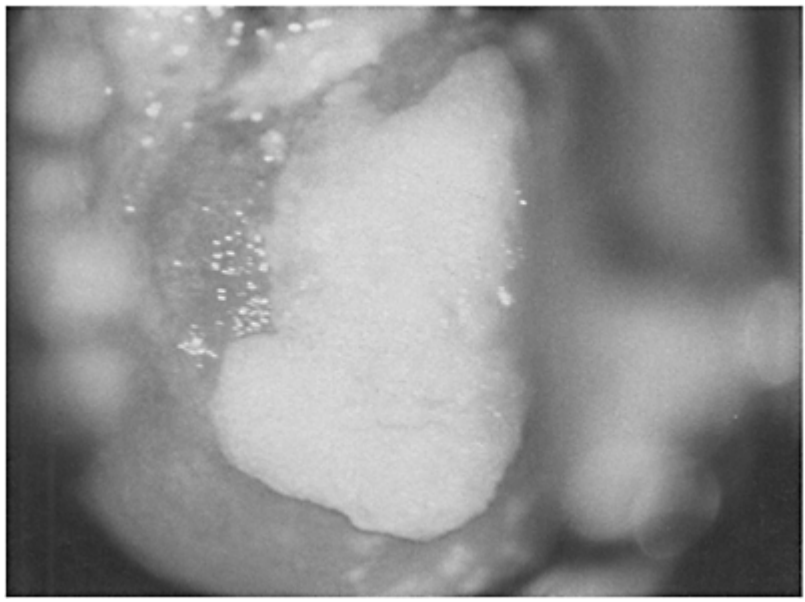

Figure 15.2 Condyloma acuminatum of the cervix after application of acetic acid

Table 15.2 Association of HPV types and cervical malignancies

Risk	***HPV types***
High-risk HPV	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Low-risk HPV	6, 11, 40 42, 43, 44

be integrated into the host genome to induce transformation and persists in productive keratinocytes as self-replicating extra/chromosomal nuclear plasmids. Integration of HPV into the host genome has been associated with malignancy (Table 15.2). HPV DNA sequences can be found in basal layer keratinocytes but complete viral particles are found only in terminally differentiated cells in the superficial layers of the dermis.

The DNA regions with protein coding potential are termed open reading frames (ORFs) which are divided into early and late capsid ORFs. The remainder of the circular viral DNA (15%) is a non-coding segment termed the upstream regulatory region (URR) located between the end of the ‘late’ region and the beginning of the ‘early’ region. ORFs E6, E7, and E8 appear responsible for oncogenic transformation and logically receive considerable investigative attention. ORF E1 specifies proteins required for regulated episomal (non-integrated) DNA replication. ORF E2 encodes proteins that regulate viral transcription, and ORFs L1 and L2 encode the major and minor capsid proteins, respectively.

With benign and precancerous HPV-related lesions, the viral DNA tends to be episomal (i.e. a free, self-replicating, extrachromosomal, circular nuclear plasmid). In invasive cancerous lesions, it is integrated (i.e. spliced into the host chromosomes by covalent bonds). This phenomenon occurs in particular with HPV 16- and HPV 18-containing tumors. Altered unregulated expression of E6 and E7 ORFs is hypothesized to be a consequence of viral integration into the host genome.

Table 15.3 Colposcopic index

Colposcopic sign	***Zero points***	***One point***	***Two points***
Margin	Condylomatous or micropapillary contour. Indistinct acetowhitening. Flocculated or feathered margins. Angular or jagged margins. Satellite lesions and acetowhitening beyond transformation zone.	Regular lesions with smooth, straight outlines.	Rolled, packing edges. Interval demarcation of appearances.
Color	Shiny-snow white color. Indistinct acetowhitening.	Intermediate shade (shiny gray).	Dull oyster-white
Vessels	Fine-caliber vessels. Poorly formed patterns. Condylomatous micropapillary lesions.	Absent vessels. Punctuation or mosaic.	Definite
Colposcopic score			
1–2=SPI or CIN 1; 3–5=CIN 1, 2; 6–8=CIN 2, 3 ‘aneuploid lesions’			

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EPIDEMIOLOGY

Human papillomavirus (HPV) infections of the genital tract are one of the most common sexually transmitted viral infections. Both the incidence and prevalence of genital HPV infection are increasing. A survey of private office-based physicians showed consultations for genital warts increased 580% in a decade. With an increasing awareness that many HPV infections are subclinical, most reports seriously underestimate the frequency of HPV infection.

Cervical cytology and histology have been used to estimate the prevalence of genital HPV infection. These studies have shown cytologic evidence of HPV infection in 1.85 to 3% of unselected Papanicolaou smears.

Routine cervical cytologic examination alone is inadequate for diagnosing all cervical HPV infections. HPV DNA sequences have been detected in greater than 50% of women attending an STD clinic who had normal Pap smears and normal colposcopic

examination. In Seattle, cervical HPV infection diagnosed by Pap smear, immunoperoxidase stains or DNA hybridization was detected in 18% of non-selected women attending an STD clinic.

In an important study from the University of California health service, women presenting for non-gynecologic complaints had a cervical and vulvar scrape for detection of HPV. Polymerase chain reaction (PCR) analysis showed that 32% of scrapes from the cervix and 42% of scrapes from the vulva were positive for HPV.

An effort to identify asymptomatic HPV infection in males has been initiated but has not been well accepted by patients or the medical community. Diagnostic methods include koilocytosis of exfoliated uroepithelial cells, tissue biopsies, and acetowhitening of penile skin viewed through a colposcope (Table 15.3). In one study of male partners of women with condyloma acuminatum, of the 88% who had histologic evidence of penile condyloma, 16% had visible lesions and 72% had asymptomatic infection detected colposcopically after application of 5% acetic acid.

The male:female ratio of genital HPV infection varied from 1:1.7 to 2:1 with the peak age at 20 to 24 years.

Sexual transmission of HPV is the commonly accepted mode of transmission. Transmission rates vary from 59 to 95%. Infectivity of genital warts may decrease with time so warts present for greater than one year may be less likely to be transmitted than warts present less than one year. Genital warts in children have been associated with child abuse but are not necessarily confirmatory for sexual contact.

ASSOCIATION OF PAPILLOMA VIRUS WITH MALIGNANCY

The association between HPV infection and genital malignancy has been investigated most intensively for cervical neoplasia, but associations exist between HPV infection and vulvar, vaginal, anal and penile neoplasia. Malignant degeneration in vulvar and anal warts has been recognized for many years but is an uncommon complication and even reportable. The concern today is not the rare event of malignant degeneration in anal and vulvar warts, but the concept that HPV can act as a carcinogen and/or co-carcinogen throughout the genital tract and that simple HPV infections should be taken seriously by the patient and clinician.

The potential role of HPV in the etiology of neoplasia was originally suspected following observations of malignant conversion of HPV-induced skin and mucosal tumors. HPV DNA was first detected in squamous cancers arising in epidermodysplasia verruciformis (a disease of multiple flat warts of nongenital skin in persons with congenital impairment of cellular immunity). The HPV DNA found in these cancers was types 5 and 8 in more than 90% of patients. An average of 20 years elapsed between the onset of verrucosis and cancer and the preferential location of carcinomas on sunlight-exposed skin implied that malignant conversion depended on the activity of other cocarcinogens.

The association of HPV infection and cervical neoplasia was first reported with the finding that koilocytes, a possible marker for HPV infection, were present in 70% of cytologic and biopsy specimens showing cervical intraepithelial neoplasia (CIN) (Figure 15.3). It has also been recognized that as the grade of CIN increases, the detection of

koilocytes decreases and they are absent in frank carcinoma. Similarly, the detection of HPV antigens show a similar decrease in higher grades of CIN. It is believed that permissive factors for productive viral infection are absent in higher grades of dysplasia and carcinoma. However, HPV DNA has been found in all grades of CIN as well as invasive cancer. The association with cervical neoplasia is strong with as many as 91% CIN lesions containing HPV DNA compared to 10% of controls.

HPV DNA types are not equally present in neoplastic lesions. Types 16 or 18 are present in 70% of cancers with types 10, 11, 31, 33, 35, 51 and 56 present in small percentages. However, types 16 and 18 are found in only a small percentage of genital warts while type 6, the most common type found in genital warts, is found much less often in genital cancer. This has led to the concept of 'high-risk' HPV types. The finding of HPV types 16 and 18 in genital lesions anywhere in the genital tract implies a greater tendency toward advanced grade neoplasia (as high as 85% in one study). The corollary is that the finding of HPV DNA type 6/11 indicates the lesion will usually not progress but will regress.

There seems to be an anatomic site selection for various HPV types. Types 16 and 18 seem to be detected in cervical neoplasia while HPV types 6 and 11 are more frequently found in the lower vaginal and vulvar lesions as well as in subclinical infection. More recently, data has been published that suggests that many HPV lesions contain more than one HPV type. Therefore, many lesions may contain both a 'high-risk' HPV DNA type 16 or 18 in addition to a 'low-risk' type 6 or 11. This suggests multiple infection or superinfection and complicates the clinical management based entirely on HPV DNA typing results.

Approximately 40% of patients with HPV disease have multiple HPV types present in their genital tissues. It has been postulated that the biologic activity of the HPV disease is determined by the HPV type. The biologic effect of multiple HPV types being present simultaneously is completely unknown.

It has now been determined that about 90% of invasive cervical squamous carcinomas contain HPV DNA. The viral DNA has been detected both in primary and metastatic cancers with HPV-16 the most prevalent type. Equally interesting is the finding of HPV DNA in histologically normal genital tissue in women with invasive carcinoma. This helps to confirm the concept that HPV infection is a generalized lower genital tract epithelial infection and not localized to the area of the genital wart or the CIN lesion and the therapy must be commensurate with the extent of the lesion.

CLINICAL MANIFESTATIONS

Clinical vs. subclinical

The extent and spectrum of genital HPV infection has not been fully appreciated by patients or by most clinicians. The spectrum of the disease has become much broader than previously recognized because of newer diagnostic tools such as HPV DNA typing and the application of the colposcope for the detection of subclinical disease. Many clinicians still regard the presence of a vulvar condyloma as a nuisance local problem and do not consider its potential presence throughout the genital tract. HPV infection must be

considered an infectious disease that in many cases will be present throughout the genital tract. Acceptance of this concept will significantly improve the chances for diagnosis and application of appropriate therapy techniques.

Vulva

The incidence of vulvar condylomata has increased 460% in the United States in the last 15 years. Age incidence is similar to other STDs with peaks at 16–25 years. Vulvar condylomas appear as pink, whitish or pigmented sessile tumors with the surface of lobulated or pointed finger-like projections. The most common sites are the posterior introitus, perineal skin, labia minora, labia majora, and urethral orifice. Less common sites are the anus, clitoris, mons pubis and crural folds. Small sessile warts or flat condyloma-like lesions which are minimally elevated, pink papules and plaques with a smooth surface may be missed during routine examination.

Generally, the majority of women with type 6 or 11 infection will not experience local complications. There is a direct association with HPV infection in the vagina and cervix and, therefore, colposcopic examination is indicated as well as careful cytological surveillance.

Subclinical vulvar HPV infection may be detected by colposcopic examination of the vulva after application of 5% acetic acid. The acetic acid removes the surface mucus and causes the individual cells to swell, giving a white color to warty or neoplastic epithelium. Colposcopic patterns involve three distinct types of SPI (subclinical papillomavirus infection). These are the presence of vestibular papillae, fused papillae or acetowhite epithelium.

The vestibular papillae are small, multiple villous projections largely confined to mucous membranes. Each villous projection resembles the individual aspirates of an exophytic condyloma. Histology will show a central capillary surrounded by koilocytotic dyskeratotic epithelium.

Fused papillae refer to individual papillae that have grown together, giving the vulvar skin a granular rather than villous appearance. These areas will show whitening with acetic acid and are associated with burning vulvar discomfort erroneously attributed to chronic *Candida albicans* infection.

Acetowhite epithelium is flat normal-appearing epithelium which turns white with application of 5% acetic acid. This may be found in vulvar areas and may act as a reservoir for high-risk HPV types. Acetowhite epithelium is usually multifocal.

Vagina

HPV infection in the vagina has been given less attention than vulvar or cervical because the lesions:

(1) seem to be asymptomatic;
(2) seem to have less malignant potential;
(3) may be more difficult to diagnose; and
(4) are more difficult to treat satisfactorily.

Vaginal condylomas can be detected in as many as one-third of patients who have vulvar condylomas.

The condylomas are usually present in the upper and lower one-third with 'high-risk' DNA types more frequently found in the upper one-third and 'low-risk' DNA types found in the lower one-third. Condylomas in the vagina are usually multiple. The lesions are small raised dense white elevations with small aspirates. Although vaginal condylomas may be asymptomatic, vaginal discharge and pruritus frequently accompany the infection. In patients with recurrent episodes of bacterial vaginosis or monilial vaginitis, the presence of HPV infection should be investigated.

Subclinical vaginal HPV infection is more common than overt condyloma. Most changes can be seen with the colposcope after application of 5% acetic acid. In addition, staining the vaginal walls with Lugol's solution will aid in making the diagnosis.

A common lesion consists of elongated vaginal papillae, made up of clustered epithelial projections with a central capillary. These lesions are analogous to the fronds seen in classic condyloma. Histologic features include koilocytotic atypia and dyskeratosis. Capsid antigen is present in 30% indicating infectivity.

A second colposcopically detectable lesion is acetowhite epithelium following 5% acetic acid application. Sharply demarcated areas of flat white epithelium are detected. Vascular patterns may be present and the small capillary loops are of uniform caliber. This lesion is more common in the upper one-third of the vagina. Punctuation and mosaicism are quite common in the upper vagina.

A third and most common colposcopically detectable lesion is that of 'reverse punctuation'. This is defined as a diffuse pattern of minimally elevated white dots against the pink background of the vaginal mucosa. The appearance is made more prominent by staining with quarter-strength Lugol's solution. The parakeratotic 'dots' will turn yellow. Histologic findings include minimal basal hyperplasia, mild koilocytosis, variable dyskeratosis and prominent intraepithelial capillaries.

Cervix

Condyloma acuminatum of the cervix was described as a rare entity in 1921 but clinically apparent lesions can now be seen in 20% of HPV-infected women. These lesions are recognized by papillary projections often with irregular vascular loops beneath the epithelium. HPV infection is usually detected within the transformation zone but can involve the original squamous epithelium of the portico.

Subclinical cervical HPV infection is generally accepted as being most common and becoming visible with application of acetic acid. Cervical HPV infection is one of the commonest STDs. The cytopathic effects of HPV include koilocytotic atypia, dyskeratosis and multinucleation.

Colposcopic differentiation of SPI and significant grades of CIN can be difficult. A colposcopic index devised by Reid and Scalzi aids in the process by using four colposcopic signs (lesion margin, color, vascular patterns and iodine staining) as a means to direct biopsies to the most severe areas (Table 15.3). SPI represents the earliest stage in the CIN continuum that leads to invasive cancer. The evidence is strong that women with koilocytotic atypia on Pap smear will show CIN and that approximately 25% will progress to CIN 3 within 2 years. The spontaneous regression rate is low (11%). The

transit time to CIN 3 today for these groups of women is shorter than that described twenty years ago and probably reflects the impact of HPV on the process.

Anus

Clinical vulvar condylomas extend into the anal canal and perianal region in about 18% of women. Lesions can be found above the dentate line in the lower rectum. Growth in the perianal region tends to be luxuriant, painful and difficult to treat.

Subclinical infection is common and 5% acetic acid should be applied prior to colposcopic evaluation. Histology shows characteristic HPV infection.

DIAGNOSIS OF HPV INFECTION

The diagnosis of HPV infection may be easy or very difficult. Diagnostic techniques include physical examination, colposcopy, cytologic studies, histologic studies, HPV antigen detection, ploidy studies of HPV DNA molecular hybridization, pdymerase chain reaction (PCR) assay, hybrid capture and Southern and dot blot.

Southern blot and dot blot use radioactive probes and are labor intensive. They require significant sample size. DNA hybridization involves non-radioactively-labeled DNA probes. It can be performed on formalin-fixed paraffin-embedded tissues and requires little specialized equipment.

Physical examination of the genital tract is simple and noninvasive. However, this method alone fails to detect most cervical HPV infections and an unknown proportion of vaginal, vulvar, anal and penile lesions.

If wart-like lesions are present on the vulva, visual diagnosis is 90% correct. It is appropriate to initiate therapy on the basis of visual diagnosis. However,

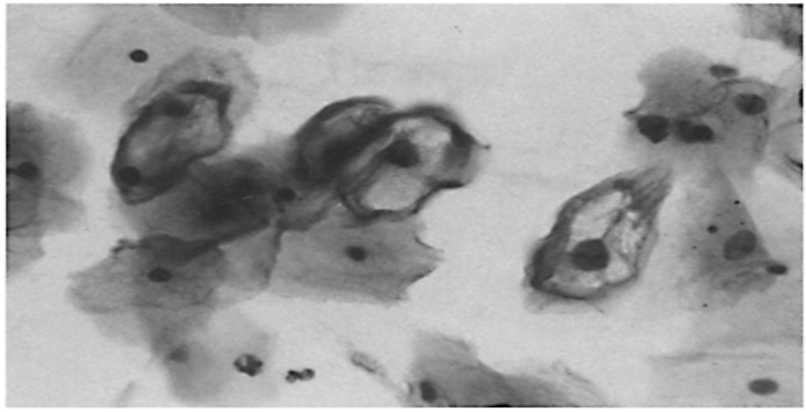

Figure 15.3 Koilocytotic changes demonstrable on cytologic smears (Papanicolaou’s stain, ×490)

should the patient fail to respond to therapy or the ‘warts’ (1) appear atypical, (2) be pigmented or change color, (3) be fixed to underlying tissues, (4) exceed 1 cm (possible Buschke-Lowenstein growths) an excisional biopsy should be seriously considered.

The differential diagnosis includes:

(1) normal anatomic structures;
(2) vestibular papillae;
(3) sebaceous glands;
(4) molluscum contagiosum;
(5) seborrheic keratoses;
(6) lichen planus;
(7) skin tags;
(8) melanocytic nevi;
(9) condyloma latum.

Colposcopic examination after application of acetic acid is time consuming but detects most of the SPI. The colposcope will help the clinician find the areas which need to be biopsied. The colposcopic examination must include the vulva, vagina, cervix and anus. The entire area should be exposed to acetic acid for at least five minutes prior to examination.

Cytologic studies are a relatively inexpensive method of diagnosing HPV infection on epithelial surfaces from which exfoliated cells can be obtained (Figures 15.3). The cytologic findings of koilocytosis, dyskaryosis, atypical parabasal cells and multinucleation can be seen. Anal cytology has been demonstrated to be useful in screening of anal HPV infection while urinary cytology was not useful as a screening procedure for HPV infection in male consorts of women with genital warts. It is not known whether penile or vulvar cytology is useful or practical.

The histologic findings of genital warts are basal cell hyperplasia, acanthosis, papillomatosis, koilocytosis, parakeratosis and mild nuclear atypia (Figures 15.4, 15.5 and 15.6). Koilocytosis is probably the most specific marker for HPV infection; however, the

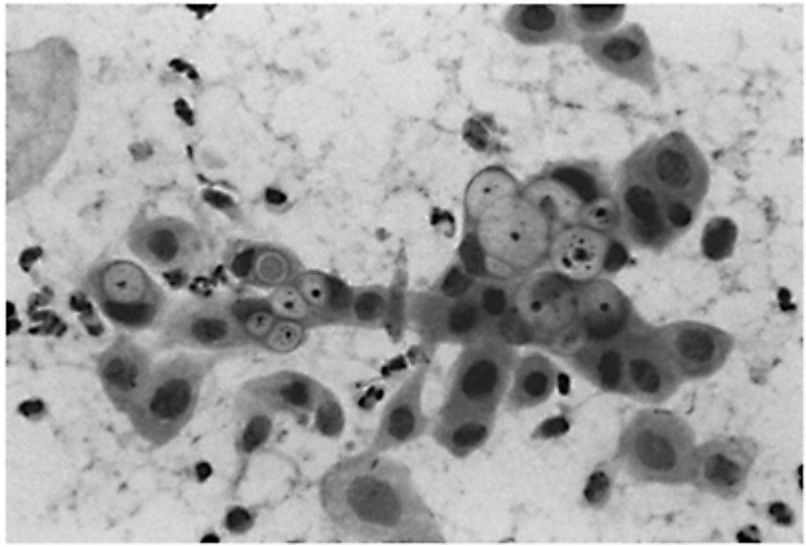

Figure 15.4 Koilocytotic changes involving glandular cells (Papanicolaou's stain, ×360)

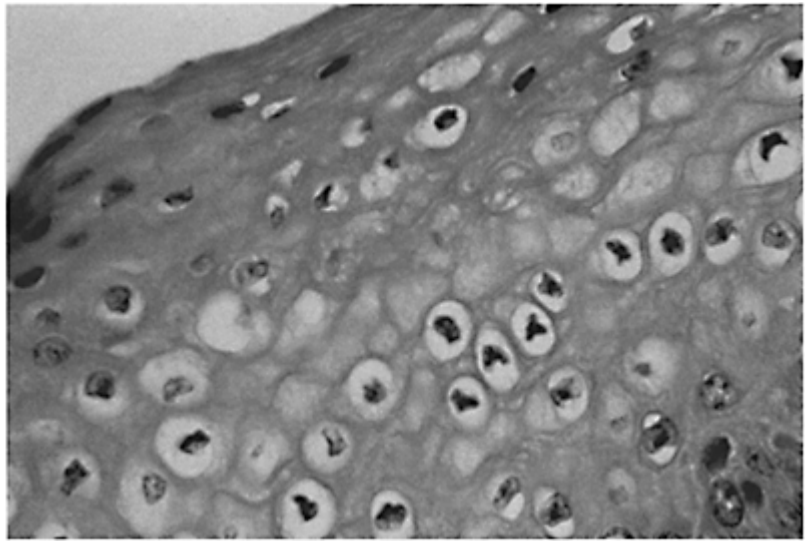

Figure 15.5 Histological demonstration of koilocytes with variable dyskeratosis (H&E stain, ×375)

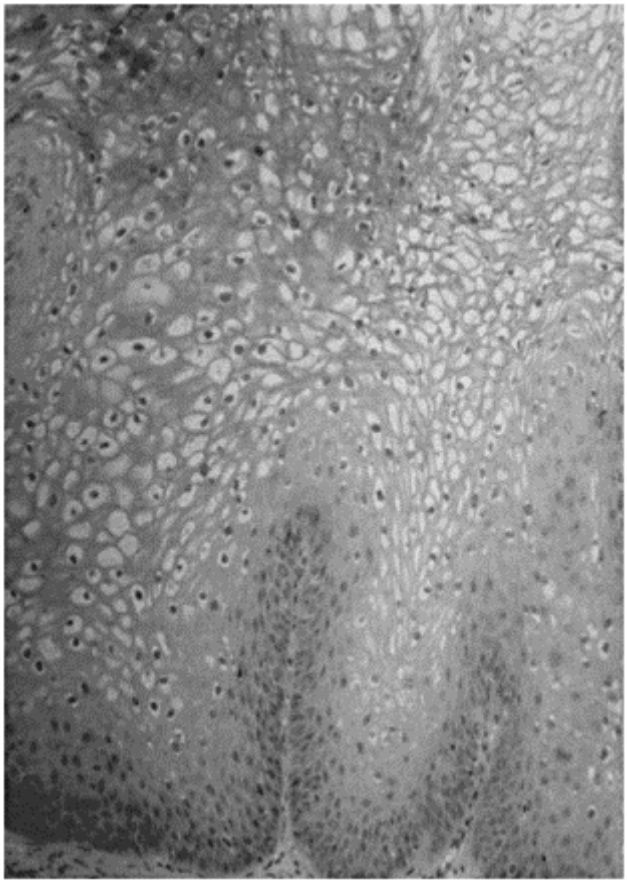

Figure 15.6 Elongated rete ridges with extensive koilocytotic change (H&E stain, ×220)

specificity of koilocytosis is poor for lesions caused by HPV DNA types 16 and 18, especially in advanced grades of CIN.

HPV antigens can be detected in cytologic or histologic specimens by immunoperoxidase staining techniques utilizing antisera made in rabbits immunized to bovine papillomavirus. The cells carrying the virus are well-differentiated keratinocytes and often koilocytes. As the dysplasia becomes progressive, it becomes increasingly difficult to detect HPV antigens. Similarly, lesions containing HPV 16 and 18 have poor sensitivity for detection of HPV antigens.

The diagnostic test which gives the clinician the most information is the isolation and cloning of HPV DNA. This has led to a typing scheme already discussed. HPV DNA has been found to be present in subclinical and overt warts, Bowenoid papules, lesions of CIN, and invasive genital cancers. Although currently a research tool, it seems to be able

to provide additional information about the type or types of HPV present in the patient. This will alert the clinician to 'high-risk' types present and should stimulate a more aggressive approach to therapy. Ploidy analysis has been utilized to attempt to predict the course of the clinical lesions. Generally, cells thought to be euploid or polyploid has been considered to be benign while cells showing aneuploidy have been thought to either be malignant or have strong malignant potential. Studies relating ploidy to progression of histologically proven SPI have been conflicting. This confusion is probably the result of the methodology currently used. This technique will probably emerge to be useful clinically. The newest technique available for diagnostic evaluation is the use of the PCR. Specific oligonucleotide primers are used to amplify segments of HPV DNA. The method is a highly specific and sensitive method of detecting HPV infection.

THERAPY FOR HPV INFECTION

The classic standard therapy for genital warts has been based on the assumption that the grossly visible warty tissue needed to be destroyed and that the virus resided only where the warts existed. The recognition of subclinical disease in addition to overt disease and the association with genital neoplasia forces a re-evaluation of the standard approach. HPV infection must be regarded as having the potential for infecting the entire genital tract, and only very early disease tends to be localized. Therapy is also complicated by the fact that HPV may be present in normal skin and in colposcopically, cytologically and histologically normal epithelium. Wart recurrence after any therapy is common and whether a virologic 'cure' can be accomplished is unknown. Practically all clinical trials address only overt visible disease. Wart recurrence after therapy is difficult to assess. It is not known whether recurrence indicates failure of therapy, failure to treat all areas involved, resistant virus or reinfection. Most recurrences are seen within 3 months of therapy. If disease is present for six months despite repetitive attempts at therapy, it is called resistant and persistent. Therapy uses agents that are keratolytic (podophyllin, tri- or bichloracetic acid, 5-fluorouracil (5-FU)); physical agents (electric cautery, laser therapy, cryotherapy) and immunotherapy (vaccine, interferon inducers). Since the classic standard approach must be modified to account for subclinical infection and the frequent presence of HPV throughout the genital tract, no single or combination of agents has emerged as standard treatment at this time.

Options

Currently available treatments for visible genital warts are patient-applied therapies: podofilox (Condylox®) and imiquimod (Aldara®); and provider-administered therapies: cryotherapy, podophyllin resin, trichloroacetic acid (TCA), bichloroacetic acid, interferon (Intron, Alferon), and surgery. Most patients have one to ten genital warts with a total wart area of 0.5 to 1.0 cm^2, which is amenable to most treatment modalities. Factors that may influence selection of treatment include wart size, wart count, anatomic site, wart morphology, patient preference, financial cost of treatment, and clinician's experience. It is important to have a treatment plan or protocol since many patients will require a course of therapy rather than a single treatment. The treatment should be no worse than the

disease. In general, warts on moist surfaces and/or located in intertriginous areas respond better to topical treatment such as TCA, podophyllin, podofilox and imiquimod than do warts on drier surfaces.

After utilization of provider-administered treatments, if there has not been significant improvement after three treatment sessions, or complete clearance after six treatment sessions, the treatment modality should be changed. The risk-benefit ratio of treatment should be evaluated throughout the course of therapy in order to avoid over-treatment. Providers should be knowledgeable about, and have available to them, at least one patient applied and one provider administered modality.

When employed properly, complications of wart treatment are rare but can occur. Scarring in the form of persistent hypo- or hyperpigmentation may occur with ablative modalities. Depressed or hypertrophic scars are rare but can occur especially when the patient has not had sufficient time to heal between treatments. Overly aggressive treatment can result in disabling chronic pain syndrome such as vulvodynia or hypoesthesia of the treatment.

Patient-applied

Podofilox 0.5% solution or gel (Condylox®)

Podofilox, being an antimitotic, causes localized tissue necrosis. The 5% solution or gel does not contain the mutagenic flavanoid compounds found in the providerapplied analogue, podphyllin. Patients may apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice daily for three days, followed by four days of no therapy. This cycle may be repeated as necessary for a total of four cycles. Total wart area treated should not exceed 10 cm^2, and a total volume of podofilox should not exceed 0.5 ml per day. If possible, the healthcare provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. The use of podofilox is contraindicated during pregnancy. Between 45% and 82% of patients treated for 4 to 6 weeks achieve total clearance of warts; however from 10% to 90% can be anticipated to experience recurrences.

Imiquimod 5% (Aldara®) cream

Imiquimod is a topically active, non-nucleoside, heterocycline amine, immune-response enhancing agent. It is a potent inducer of interferon-alpha and other cytokines. Patients should apply imiquimod cream with a finger, at bed-time, three times per week, for up to 16 weeks. It is recommended that 6–10 hours following the application, the treatment area be washed with mild soap and water. Many patients may be clear by 8–10 weeks or sooner. **The use of imiquimod is contraindicated in pregnancy.**

This therapeutic approach is unique in that the host's cell-mediated immunity is used to destroy the warts. Imiquimod is used to sensitize the patient and when this is accomplished, the imiquimod is placed in a cream which is placed on the wart. A delayed hypersensitivity reaction occurs destroying the wart. The difficulties of therapy include an inability to sensitize the patient, varying sensitivity with potential for severe reaction, and the patient's resistance to a hypersensitivity reaction in the perineal area.

Between 37% and 85% of patients treated with 5% cream exhibit wart clearance after therapy. Between 13% to 19% of these patients can be expected to have recurrences.

Provider-administered

Cryotherapy

Cryotherapy causes cryocytolysis, resulting in tissue sloughing. Cryotherapy of anogenital warts employs either single or repetitive 1–2 minute freeze-thaw cycles to destroy wart tissue. Cryotherapy may be performed by probe or liquid nitrogen. Most patients require 3 to 6 treatments to clear the warts. In comparative studies, cryotherapy is more effective than podopyllin and is as effective as electrical cautery and laser therapy. Between 60% and 97% will have total clearing for 3 to 6 weeks. Wart recurrences may occur in 20–79% of patients so treated.

Keratolytic agents

Podophyllin resin 10–25% This is in a compound tincture of benzoin. Podophyllin is an extract from May apples and there are four active ingredients which vary in concentration in different lots of podophyllin. It acts by poisoning the mitotic spindle and causing intense vasospasm. A small amount should be applied to each wart and allowed to air dry. To avoid the possibility of problems with systemic absorption and toxicity some experts recommend that application be limited to $\leq$0.5 ml or $\leq$10 cm^2 of warts per session.

The patient is instructed to wash off the podophyllin in 4–6 hours. It is applied to warts weekly until the wart disappears. The side effects are unpredictable and include severe local reaction at initiation and ulceration and systemic toxicity from excessive absorption. Podophyllin is contraindicated in pregnancy because of teratogenesis and possible carcinogenesis.

Podophyllin's success is dependent on the size and number of lesions and is indicated in patients with minimal vulvar or anal disease. It is generally not used for vaginal or cervical HPV infection. Its use has diminished significantly.

Trichloracetic acid (TCA) (bichloracetic acid) 80–90%

The mode of action of TCA is by precipitation of surface proteins and, therefore, it is less effective when applied to keratinized epithelium. It should be used at a strength of 85%. Application should be via small cottontipped applicator. It is not necessary to apply paraffin to adjacent skin as this is cumbersome and counterproductive. Powder with talc or sodium bicarbonate (baking soda) is used to remove unreacted acid if an excess amount is applied. TCA has been used on occasion on lesions of the cervix and seems to be well tolerated and effective. However, no randomized clinical trial of TCA therapy of cervical HPV disease has been published. Clearance rates between 50% and 100% have been reported. Between 6% and 50% of patients so treated may develop recurrences.

5-Fluorouracil

This agent is a pyrimidine antimetabolite that causes necrosis and sloughing of growing tissue. The 5% 5-FU cream is applied by several protocols:

(1) **Vulvar or anal lesions:** 5-FU is applied directly to the lesion on a daily basis until erythema to vesiculation occurs. This will generally occur on about the 7–10th day of therapy. The course may be repeated to any remaining lesions following initial healing. A preferable alternative therapy is the administration of 5-FU on two consecutive days each week for 10–12 weeks. This seems to diminish the inflammatory reaction which results from 7–10 days of consecutive therapy.
(2) **Vaginal lesions:** 5-FU may be applied via vaginal applicator with an applicator full applied nightly for 7 days or until an inflammatory reaction occurs. A vaginal tampon should be placed at the introitus to prevent the 5-FU from getting to the vulva.

A preferable alternative method is to use 5-FU once weekly for 10–12 weeks to diminish the vaginitis from the more intensive course of therapy. This has been found to be equally effective as the more intensive course. Randomized, placebo-controlled studies have demonstrate total wart clearance in 55% to 65% of patients. Between 30% and 45% of patients will have recurrences within three months after the completion of therapy.

5-FU is a mutagen and **is contraindicated in pregnant and lactating women**.

Surgical removal

Tangential scissor excision, tangential shave excision, curettage, or electrosurgery have all been utilized with varying degrees of success.

Laser therapy

Laser therapy is widespread and has the theoretical advantages of precise control of depth, margins, and hemostasis. Laser ablation has the disadvantages of being under operator control as well as being able to treat only visible disease. Recurrences occur in 25 to 100% of cases. Some clinicians have extended their field of treatment to account for latent HPV at the margins, but more than one-half of these women have recurrences and the morbidity is excessive. The use of 5-FU immediately following laser therapy of the vagina has been proposed, in which 5-FU is placed intravaginally daily for 5 days. The success and morbidity rates need to be confirmed. The use of electrical cautery destruction of warts has been found to be very effective. It is particularly useful for office destruction of small lesions. It may be used for larger warts but the laser offers more precision.

Immunotherapy

Interferons are a family of proteins with antiviral, antiproliferative and immunomodulatory properties. Interferon has been shown to induce reversion of BPV-transformed mouse cells and elimination of extrachromosomal viral DNA.

Leukocyte interferon, alpha-recombinant interferon, beta interferon and lymphoblastoid interferon have been used in the treatment of warts topically,

intralesionally and systemically. Generally speaking, the topical therapy is least effective; intralesional therapy is effective for a small wart number or volume; and systemic therapy is effective for large wart numbers and volumes and especially for intravaginal warts. Although the preparations of interferon doses and treatment regimens varied, the studies have reported positive results; however, only the responses of clinically overt lesions have been evaluated. The potential advantages of therapy with systemic interferon include therapy of all wart-affected areas at the same time, the potential of eliminating the HPV from the patient, and lower morbidity than other techniques. Interferon is administered parenterally either by intralesional or subcutaneous routes. The intralesional route is recommended by the package inserts and has FDA approval. This route is very painful to the patient because wart tissue is very dense and distention with even small amounts of interferon is very uncomfortable. The usual scenario that occurs is the clinician injects the wart intralesionally with the first injection; however, on the subsequent injections the clinician places the interferon under the wart, i.e. subcutaneously, and therefore the injection is painless. We have found that a superior method without the loss of efficacy is the patient's self administration of interferon subcutaneously in the anterior thigh. The administration is with a 29 gauge needle and TB syringe. The dosage of interferon should be 2.5 or 3.0 million units three times per week for 8 weeks. The patient should have a complete blood count with platelets, and liver function tests determination prior to initiation of interferon. If the pulmonary tests are normal, no additional testing is necessary. This program will result in a clearing of the condyloma in 65% to 70% of the patients. Follow-up data from patients achieving a complete clearing of the condyloma had a recurrence rate of <5% in 2 years.

Side effects are dose dependent and are minimal at 3 million units three times per week. Side effects will

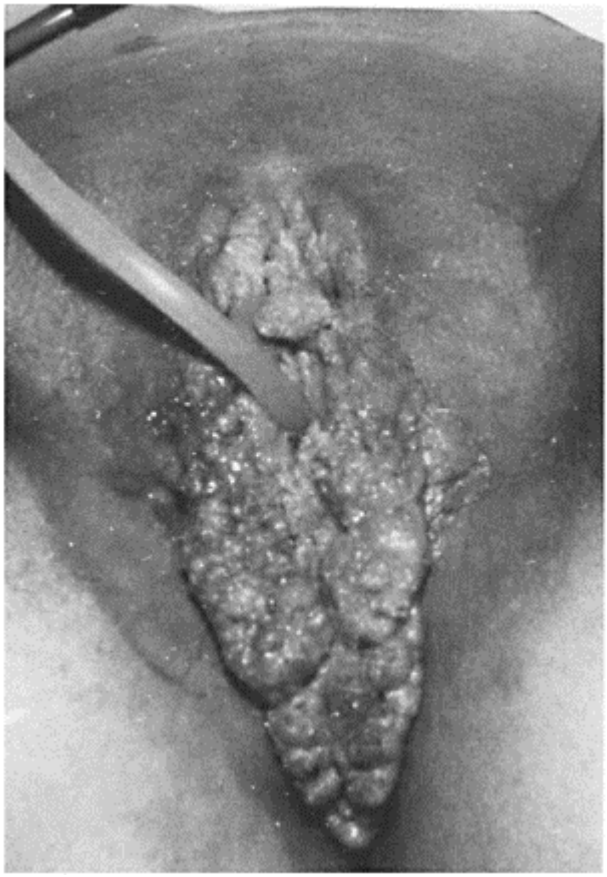

Figure 15.7 Extensive fused vulvar condyloma in pregnancy

occur in less than 10% of patients at this dosing level. The most frequent side effects at this dose level are transient malaise, fatigue, and headache. Experience with interferon therapy has shown that if any external genital warts remain after 8 weeks of therapy interferon may be continued for another four weeks. An alternative therapy for condyloma at the conclusion of the primary interferon course is the use of CO_2 laser, cryotherapy or surgical excision. The combination of laser ablation as primary therapy plus interferon 1.0 million units three times per week for ten weeks may be successful for the patient who wants immediate wart removal.

Therapy of HPV in pregnancy

The true incidence of genital HPV infection during pregnancy is unknown but it is probably greater than in the general population. Existing lesions tend to enlarge during

pregnancy, probably in response to diminished cell-mediated immunity (Figure 15.7). These lesions may become large and friable causing pain and hemorrhage. The fetal effects are those of the possibility of passage of HPV to the fetus during delivery. Congenital, infant and childhood genital condylomas have been reported in children born to mothers known to have genital warts; however, it is unknown how many pregnant women harbor HPV. The number of children with respiratory papillomatosis is low. Recent data from the Perinatal Collaborative Study reported no cases in a 7-year follow-up of 44000 deliveries.

Therapy with podophyllin is contraindicated in pregnancy because of toxicity and teratogenesis. Agents such as bleomycin and 5-fluorouracil are also contraindicated because of their antimitotic and cytotoxic action. TCA (85%) solution is useful and can be applied weekly either to skin or mucous membranes. Cryotherapy and CO_2 laser have been found to be helpful in reducing the number and volume of warts. Most of the time the warts will diminish significantly after delivery.

IMPACT OF HIV ON HPV

The concomitant epidemic of HIV and HPV more than overlap each other. Findings from a number of clinical studies suggest that while HPV does not appear to alter the course or frequency of HIV infections, HIV-induced immunosuppression does increase the severity and duration of anogenital warts. Also, it is probable that it increases the period of infectiousness and decreases the probability of a good clinical response to conventional therapy. The impact of HIV on HPV pathogenesis appears to extend beyond increased clinical recognition of conventional lesions and severity of disease. If demographic studies are correct, pre-invasive and ultimately invasive cervical neoplasia are becoming more common manifestations in patients with dual infections.

The magnitude of host immunosuppression influences the probability of pre-malignant and/or preinvasive histological changes. Spinillo *et al.* evaluated the prevalence of lower genital neoplasia and HPV-related genital lesions in each cohort of 75 women infected with HIV-1 at different stages of the disease. The overall rate of CIN in the group studies was 29.3% (22/75). Eight out of ten high-grade CIN lesions contained 'high-risk' HPV-DNA 16/18 and/or 31/35/51 as demonstrated by *in situ* hybridization with biotinylated probes. Vulvar and/or perianal condylomata were histologically diagnosed in 14 patients (18.7%); nine of these biopsies contained detectable HPV-DNA which was always related to HPV6/11.

The rate of high-grade CIN-symptomatic HIV-infected patients was 28% (7/25), compared to 6% (3/50) of the other cases (p=0.02). CD4+ lymphocyte counts, white blood cell counts, the CD4+/CD8+ cell ratio and the percentage of CD4+ lymphocytes were lower in patients with high-grade CIN than in patients with negative colposcopical and/or cytological examinations. After adequate standard treatment (cryotherapy, electrocauterization, cold-knife conization), only one case of CIN 2 recurred during the two year follow-up period. The prevalence of lower genital neoplasia and HPV-related lesions among HIV-infected women is high (compared with 9% of 76 intravenous drug users who were HIV negative and 4% of 526 new high-risk women) and therefore seems to correlate with the severity of HIV disease.

Johnson *et al.* correlated HPV-DNA testing with CD4 T-cell status in 32 HIV-infected women using colposcopy, Papanicolaou smears, and polymerase chain reaction. Women with a CD4 T-cell count below 200/µl were considered functionally immunosuppressed. The frequency of HPV positivity was five fold higher among immunocompromised women (nine of ten) than in relatively immunocompetent HIV-infected women (four of 22). Four immunosuppressed women, compared with no immunocompetent subjects, showed evidence of HPV-DNA without signs of HPV-associated lesions by cytology or histology (i.e. latent HPV infection). Furthermore, four of the nine immunocompromised subjects, compared with four of the 21 immunocompetent subjects, had CIN. HPV 18 was detected in five of the ten women with CD4 T-cell counts below 200/µl and in only one of the 22 with CD4 T-cell counts above that level. These results suggest that impaired immune status, as reflected by the CD4 T-cell count, was an important factor in increasing the severity of HPV-induced cervical infection in their population.

HPV is not a true opportunistic infection; however, its apparent progression to cervical neoplasia can be viewed as an opportunistic complication of a concomitant infection/disease. Laga *et al.* followed 47 HIV-seropositive and 48 HIV-seronegative patients. Thirty-eight percent of the HIV-seropositive and eight percent of the seronegative women (odds ratio=6.8; p=0.001) had HPV-DNA. This was found using:

(1) Vira Type (a dot-blot assay which detects specific genital HPV types); or
(2) low-stringency Southern blot (a blot that detects all HPV types).

Eighty-two women (86%) had an interpretable Pap smear; eleven of 41 (27%) HIV-seropositive women, and one of 41 (3%) seronegative women had CIN: odds ratio=14.7; p=0.002). HPV was detected in eight of 11 (73%) seropositive women with CIN.

As many as 12% of all HIV-infected individuals develop malignant lymphoma, primarily of non-Hodgkin's B-cell phenotype. The etiology is unclear, but may be facilitated by long-term AZT therapy. HIV may be associated with reactivation of a chronic hepatitis B virus (HBV) infection, and HBV itself may induce HIV replication in latently infected cells, through its X gene. When viewed in an abstract sense, the STD wars are a collective tribute to what can be achieved as a consequence of diversity of the genetic pool. It should be a warning to those who would seek to limit genetic diversity.

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16
Human B-19 parvovirus

Newton G.Osborne, MD, PhD

Human parvovirus virus belongs to the family Parvoviridae, which includes two general DNA vertebrate viruses: genus parvovirus (autonomously replicating parvoviruses) and genus dependovirus (parvoviruses that require a helper virus, such as adenovirus or herpesvirus, for replication), and one genus of invertebrate viruses. B-19 is in the genus parvovirus, which includes a number of animal parvoviruses such as the canine parvovirus and feline panleukopenia virus. The parvoviruses tend to be species-specific; only adeno-associated parvoviruses (members of the dependovirus genus) and B-19 are known to infect humans. Animal parvoviruses are known to cause fetal infection, intrauterine death and abortion. Cerebral hypoplasia in kittens and pseudo-Down's syndrome in hamsters have been attributed to intrauterine parvovirus infection.

B-19 parvovirus, a non-enveloped, single stranded DNA virus about 20 nm diameter, is responsible for benign illness in children (fifth disease) or in adults (arthritis). Acute or chronic anemia may occur following the lysis of its target cell, the erythroid progenitors.

CLINICAL DISEASE

Erythema infectiosum (Fifth disease)

The most commonly recognized illness associated with B-19 infection is erythema infectiosum (EI). The incubation period is usually 4–14 days, but can be as long as 20 days. The individual is contagious prior to the development of a rash. Aerosol spread is the principal method of dissemination. Respiratory secretions contain the virus up to the time of onset of rash or arthralgia and rarely thereafter. EI is a mild exanthematous childhood illness which begins as a bright red facial rash ('slapped cheek' appearance), and spreads to the trunk and extremities. As it fades it produces a reticulated or lace-like appearance. Reappearance of the rash may occur for several weeks following non-specific stimuli such as change in temperature, sunlight, and emotional stress. Typically, the patient is otherwise well at rash onset but often gives a history of mild systemic symptoms 1–4 days before rash onset. In some outbreaks, pruritus has been a common clinical feature.

Maternal parvovirus B-19 infection is often atypical or asymptomatic. Asymptomatic disease occurs in approximately 20% of the cases. Rash or fever which is common in children may not develop in adults. Viremia precedes the rash.

In adults infection often produces a symmetrical peripheral polyarthropathy. Joints in the hands are most frequently affected, followed by the knees and wrists. Symptoms are

usually self-limited but may persist for several months. Joint symptoms, more common in adults, may occur as the sole manifestation of infection.

The highest rate of attack is in school age children and household contacts. Although commonly observed in children ages 2 to 12, approximately 40% of the individuals over 12 years of age are sero-susceptible.

In adult patients, particularly women, arthralgia or arthritis has been associated with up to 80% involvement. The process usually starts in the small joints of the hand and progresses to larger joints. The presence of a rash involving primarily the face, or B-19 infection in the community, should suggest the possibility of Fifth disease; however arthralgia, arthritis or arthrophy may occur in the absence of a rash.

Transient aplastic crisis (TAC)

Human parvoviruses have a special affinity for rapidly dividing cells and, in particular, marrow erythroid progenitor cells. The virus attacks immature erythroblasts, arresting red blood cell (RBC) production. Destruction of erythroid lineage cells may involve apoptosis induced by the non-structural protein of the virus. Parvovirus B-19 infections have been implicated in the induction of aplastic crisis in patients with sickle cell diseases, hereditary spherocytosis and other chronic hemolytic anemias.

Parvovirus B-19 is the primary etiologic agent causing TAC in patients with chronic hemolytic anemias (e.g. sickle cell disease, hemoglobin SG disease, hereditary spherocytosis, beta-thalassemia, and autoimmune hemolytic anemia). It can also cause TAC in other conditions in which increased red cell production is necessary to maintain stable red cell indices, as may occur in anemia due to blood loss. Patients with TAC typically present with pallor, weakness, and lethargy and may report a non-specific prodromal illness in the preceding one to seven days. Few patients with TAC report a rash. In the acute phase of the illness, patients usually have a moderate to severe anemia with absence of reticulocytes, and bone marrow examination shows a hypoplastic or an aplastic erythroid series with a normal myeloid series. Recovery is indicated by a return of reticulocytes in the peripheral smear approximately seven to ten days after their disappearance. TAC may require transfusion and hospitalization and can be fatal if not treated promptly. In immunocompromised individuals, B-19 parvovirus may cause pure red cell aplasia.

HUMAN PARVOVIRUS INFECTION AND PREGNANCY

Approximately 50% of pregnant women have serological evidence of prior parvovirus B-19 infection. Prior infection confers immunity Maternal disease is usually self-limited, but the effects to the fetus can be devastating.

Human parvovirus B-19 is a recognized cause of hydrops fetalis. Infection is accompanied by characteristic intranuclear inclusions in fixed and circulating RBC precursors. These inclusions have been shown to contain virus particles by electron microscopy and *in situ* hybridization. Recent work has shown that parvovirus B-19 can infect cells other than erythroid precursors, such as myocardial cells. Infected fetuses are not always hydropic.

Maternal infection results in increased abortion and stillbirth. Early infected fetuses are particularly vulnerable to premature demise owing to their high erythrocyte turnover rate and limited hematologic reserves. The overall risk of fetal loss following maternal exposure is much less than previously thought, and may be less than 3% in the first 20 weeks of gestation or approximately 10%, if the mother is actually infected. Although parvoviruses are teratogenic in animals, there is no evidence that B-19 is a significant human teratogen.

Parvovirus B-19 infection appears to be a significant cause of second trimester abortions. Nyman *et al.* assessed the frequency of first-trimester fetal loss associated with parvovirus B-19 infection during a nonepidemic period in Sweden. Using B-19 DNA-specific polymerase chain reaction (PCR) in placental tissue, only one of 36 placentae examined from first trimester losses contained detectable parvovirus B-19 DNA. In second-trimester fetal losses, eight of 64 samples were B-19 DNA positive.

Ananda *et al.* have reported six women with serological evidence of having contracted human parvovirus infection during pregnancy. Two of the women had mid-third trimester abortions. Both abortuses were grossly hydropic with anemia. Histopathological analysis revealed a pronounced leukoerythroblastic reaction, hepatitis, excess iron pigment in liver and degenerative changes in the hematopoietic cell nuclei. Dot hybridization with radiolabeled human parvovirus probes revealed viral DNA in several tissues of both fetuses. The remaining four women had uncomplicated pregnancies and delivered apparently healthy babies, none of whom had human parvovirus specific immunoglobulin M (IgM) antibodies at delivery.

Maeda *et al.* reported two cases of non-immunologic hydrops fetalis associated with intrauterine human parvovirus B-19 infection. In these cases, hydrops fetalis was diagnosed with ultrasound at 21 and 22 weeks' gestation after 10 or more days of maternal flu-like symptoms. The outcome was stillbirth in one case and neonatal death in the other. In both cases, intrauterine infection by human parvovirus B-19 was confirmed based on two findings: maternal serum positive for human parvovirus B-19 IgM antibody, and human parvovirus B-19 DNA detected in the fetal organs using Southern blotting and hybridization with a labeled probe. Laboratory tests on cord blood demonstrated a RBC count of 163×10^4 μl nucleated red cells numbering 1267 per 50 white cells in the live-birth case. Histologic examinations of fetal tissues demonstrated leukoerythroblastic reaction in the liver and spleen, granular hemosiderin deposition in hepatocytes and Kupffer cells, and bilirubin deposition in the intercellular space in the liver. Hydropic changes may be induced by the sudden decrease in oxygen-carrying capacity of the blood due to severe anemia caused by the infection.

Schwarz *et al.* serologically confirmed 80 acute cases of parvovirus B-19 infection in pregnancy using enzyme-linked immunosorbent assay (ELISA). Of the 80 pregnancies, 4 were terminated. Of the remaining 76 pregnancies, no fetal complications were observed in 36 (47.4%), hydrops fetalis occurred in 18 (23.7%) and no further information was available in 22 (28.9%). Fifteen of 18 (83.3%) fetuses with hydrops died. Intrauterine transfusion was performed in the remaining three fetuses and pregnancy continued without further complications.

Sheikh *et al.* reported two cases of fetal parvovirus B-19 infection with documented hydrops at 24 and 30 weeks of gestation. Serial sonograms demonstrated that the hydrops

resolved spontaneously over three to five weeks after initial diagnosis. Both infants appeared normal at birth and developed normally through the first year of life.

Hager *et al.* studied 618 pregnant women exposed to parvovirus B-19. Of the 618 pregnant women, 307 (49.7%) were immune to B-19, 259 remained susceptible after exposure and 52 (16.7% of all susceptibles) contracted B-19 infection. None of the 52 fetuses of infected women developed nonimmune hydrops, and there were no fetal deaths attributed to B-19 in this group. The risk of maternal B-19 infection in pregnancy was significantly higher when the source of exposure was her own child. Maternal symptoms of polyarthralgia (46%), fever (19%), and non-specific rash (38%) were significantly more common ($p<0.001$) in IgM-positive patients than in non-infected women (4.1%, 2.8%, and 5.7% respectively). Only 17 (33%) of the IgM-positive women were entirely asymptomatic.

In the most comprehensive study done to date, Rodis *et al.* retrospectively surveyed the progeny of 113 immunoglobulin positive women. The 113 pregnancies resulted in 103 term singletons, two sets of twins (of which one neonate died of complications of prematurity), one hydropic stillborn, four spontaneous abortions, and one ectopic pregnancy. The mean gestational age at time of exposure was 15.6 weeks. The median age of the liveborn infants in study and comparison groups was 4 years old. Eight of the 108 (7.3%) surviving children, one set of twins (exposed at 27 weeks), and six singletons (exposed at 7,8,9,20,27 and 35 weeks) had developmental delays in speech, language, information processing, and attention. Their conclusion was that while there was no apparent increase in the frequency of developmental delays in children with exposure *in utero* to parvovirus, larger studies are needed. No increased incidence of congenital anomalies was identified.

Congenital postnatal infection

Adverse fetal/neonatal consequences are not limited to erythroid cells. The virus can infect and cause disease in myocardial and endothelial cells. Neonatal cases of myocarditis, hepatitis and systemic necrotizing vasculitis have been described in infected infants.

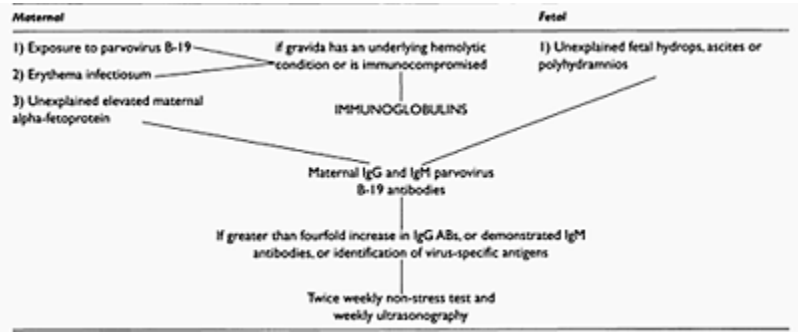
In suspected cases of fetal infection, cordocentesis can be performed. If the technology is available, B-19 infected fetal erythroblasts can be detected by standard histological staining methods and *in situ* hybridization using a digoxigenin-labeled B-19 DNA probe and PCR.

Rather than being teratogenic, intrauterine human parvovirus infection appears to be embryocidal. No increase in the incidence of anti-parvovirus antibodies occurs in malformed infants as compared with normal infants.

DIAGNOSIS

While a presumptive diagnosis can be inferred on clinical grounds, definite diagnosis requires serological confirmation. IgG and IgM titers are available through the CDC laboratories on a limited basis for women with

Table 16.1 Management of maternal/fetal parvovirus infection



clear-cut exposure to parvovirus B-19 infection during pregnancy. The most sensitive serological test to detect recent infection is the IgM-antibody assay. Parvovirus B-19 IgM antibody can be detected by capture-antibody radioimmunoassay or enzyme immunoassay in approximately 90% of cases by the third day after symptoms of TAC or EI begin. The titer and the percentage of positives begin to decline 30–60 days after onset. Maternal IgM titers may drop to low or undetectable levels depending on the interval between maternal infection and fetal signs of involvement. B-19 IgG antibody is usually present by the seventh day of illness and persists for years.

There are severall methods to diagnose parvovirus infection. They rely on antibodies to the virus, PCR for detection of the virus and histopathology.

An IgG antibody response occurs usually within a week of IgM antibody production. IgG antibody is protective and if positive in the absence of IgM specific antibodies represents past exposure. The diagnosis by antibody testing is limited by the assay and reagents employed. Assays using serum-derived or recombinant antigens are significantly better than those using peptide antigens.

PCR assays for the detection of parvovirus DNA have been developed and applied to clinical diagnosis of this disease. Amniotic fluid appears to be a good source to test for parvovius DNA by PCR for the diagnosis of *in utero* infection.

Histological studies looking for inclusion bearing cells (finding of characteristic intranuclear inclusions in nucleated erythroid cells in formalin-fixed placental or fetal tissues) can suggest the diagnosis of this infection.

Fetal/neonatal serological response to infection can also exhibit variability. Only a minority of viral DNA confirmed cases of congenital infection will have a B-19 positive response. Infants exposed to the virus earlier in gestation are less likely to produce an IgM immune response; infants infected in the last trimester almost invariably do. The most definitive way to document infection is the demonstration of viral DNA in infected tissue samples.

For women with a documented infection, maternal serum alpha-fetoprotein levels and diagnostic ultrasound examinations have been used to identify adversely affected fetuses. The sensitivity and specificity of these tests are sensitivity 94.1% and specificity 93.3%. Fetal anemia caused by parovirus infection can be detected non-invasively by Doppler

ultrasonography on the basis of an increase in the peak velocity of systolic blood flow in the middle cerebral artery.

The fetuses of gravida with only IgG specific antibodies are not at risk for the *in utero* development of non-immune hydrops. If the mother has IgM and no IgG specific antibodies to human parvovirus B-19, the fetus is at risk. One-third of the progeny may develop an aplastic crisis resulting in fetal hydrops. Current management dictates careful serological, clinical and ultrasonographic evaluation of the fetus for evidence of hydrops fetalis (Table 16.1).

Non-immune hydrops is the presence of excessive fetal body fluid accumulated in the tissues and serous cavities in the absence of RBC antibodies. Ultrasonic diagnosis includes subcutaneous edema (>5 mm), ascites, pleural effusion, pericardial effusion, excessive amniotic fluid, and placental edema (>6 cm). Hydrops fetalis can be diagnosed by ultrasonography as early as 10 to 14 days after maternal illness. The majority of fetuses that develop hydrops after maternal parvovirus infection do so within 6 to 8 weeks of infection. Weekly ultrasound studies are recommended for 8 weeks from the time of maternal infection or 6 weeks from the documented convalescent titer if the precise time of maternal infection is unknown.

When a gravida presents with hydrops, a diagnosis of parvovirus fetal infection can be made by detection of viral agents in amniotic fluid using PCR or ligase chain reaction (LCR) tests.

THERAPY

The immune response to the virus is largely humoral and directed against limited numbers of epitopes. Persistent infection is due to failure to produce neutralizing antibodies. Because viral infection is prevalent in the population, therapeutic immune globulin preparations are a good source of anti-B-19 antibodies. IgG administration can lead to cure of anemia in the congenitally immunodeficient patient and to its amelioration in AIDS patients with persistent parvovirus infection. Treatment strategies may include supportive care, analgesic medications, transfusions with RBC or administration of intravenous immunoglobulin, depending on the clinical circumstances.

Maternal therapy is largely symptomatic. Care should be given to limiting exposure to other gravida.

In the presence of hydrops at or beyond 20 weeks of gestation, diagnostic cordocentesis is recommended. The fetal blood should be tested for fetal hematocrit, reticulocyte count, platelet count, white blood cells, IgM anti-parvovirus B-19 antibodies and parvovirus B-19 DNA (using PCR).

While fetal hydrops may spontaneously regress, intrauterine transfusion is the cornerstone of management when the biophysical profile begins to change. Rodis recommends transfusing the fetus sufficient to raise the fetal hematocrit to 45%. Because fetal aplasia is transient, being related to fetal viremia, a single transfusion usually suffices. Fetal anemia with a reticulocyte count of 105×10^{9}l suggests that the fetus is in the recovery phase of the infection. These fetuses should be followed closely with fetal biophysical profiling.

At some future date, an attenuated live virus vaccine will be available. At such time, a prenatal strategy, not dissimilar to that employed for rubella may be implemented. No studies have been conducted to determine whether pre-exposure or postexposure prophylaxis with commercially available immune globulin preparations would prevent infection or modify the course of illness during community outbreaks.

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17
Influenza viruses

Influenza virus infections occur every year in the United States but vary greatly in incidence and geographic distribution. Infections may be asymptomatic or they may produce a spectrum of manifestations ranging from mild upper respiratory infection to pneumonia and death.

Influenza epidemics are frequently associated with deaths in excess of the number normally expected. More than 200000 excess deaths are estimated to have occurred in association with influenza epidemics in the United States during 1968–1982. Excess deaths in this period were attributable mainly to influenza A viruses, although influenza B epidemics were occasionally associated with excess deaths in 1979–1980.

INFLUENZA A AND B VIRUSES

Type A influenza viruses occur frequently in humans and domestic animals. These pathogens all have a core of ribonucleic acid (RNA). This internal component is antigenically stable, but the two envelope proteins of the virus may vary. The World Health Organization nomenclature for influenza A viruses includes their strain designation and a description of hemagglutinin (H) and neuraminidase (N), the two surface antigens. The presence of these two proteins provides a basis for dividing influenza A viruses into subtypes. Three subtypes of hemagglutinin (H1, H2, H3) and two subtypes of neuraminidase (N1, N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially hemagglutinin, reduces the likelihood of infection and the severity of disease if a person does become infected. However, there may be sufficient antigenic variation (antigenic drift) within the same subtype over time, so that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Although influenza B viruses have shown much more antigenic stability than influenza A viruses, antigenic variation does occur. As a consequence, the antigenic characteristics of current strains provide the basis for selecting virus strains to be included in the vaccine. Human and animal influenza A viruses are interrelated, but not identical.

Between epidemics, there are minor degrees of antigenic drift because of the passage of human influenza A viruses in partially immune people. This process selects mutants that are responsible for the seasonal illnesses experienced every year or so. Major antigenic change probably results from recombination of animal and human influenza A viruses. Influenza A virus may cross the species line periodically and cause major alterations of one or both of the envelop proteins. Laver (at Canberra) and Webster (at Memphis) have postulated that new human strains appear by recombination of viruses from animals and humans. They suggest that A2/Hong Kong/68 strain was a recombinant

that gets its N2 moiety from an Asian H2N2 strain and its H3 from another unknown donor. The influenza B viruses have no known animal reservoirs.

INFLUENZAL PNEUMONIA

Analysis of virologically confirmed fatal cases of influenza indicate three broad patterns of respiratory involvement: pure influenza-virus pneumonia, postinfluenzal bacterial pneumonia, and pneumonia due to concomitant virus and bacterial infection. In terms of their therapeutic ramifications as well as their pathogenesis, the latter two categories can be considered as one, namely, influenza-associated bacterial pneumonia. The translation of infection into mortality or into disease sufficiently severe to force hospitalization has led to early recognition of the fact that influenza constitutes a special hazard to patients with cardiopulmonary disease and to gravidas. Pure influenza virus pneumonia functions as a lethal disease almost exclusively in these special circumstances. In the 1957–1958 epidemic, influenzal pneumonia was the leading cause of maternal mortality in Minnesota, but what was more significant was the observation that gravidas died from pure influenza virus pneumonia and not from superimposed bacterial infection.

Pure influenza-virus pneumonia

A wide spectrum of modes of onset of symptoms and signs is observable with influenza virus pneumonia. Nevertheless, sufficient common denominators are discernible to permit a generalized description of the typical fatal course. Usually there is a short antecedent illness of 6–12 hours characterized by malaise, myalgia, and chilly sensation, followed by the onset of fever, headaches, pain on ocular movement, nasal congestion, or mild sore throat. Between the second and third day, cough, dyspnea, hemoptysis, and occasionally pleuritic chest pain develop. These symptoms usually herald the onset of clinical deterioration. Analysis of the white blood cell (WBC) count at this time reveals that it is either within normal limits or slightly elevated. There is no marked shift to the left in terms of the WBC differential. The cough becomes productive of frothy bloodstained sputum. Frank hemoptysis is frequent. Marked cyanosis secondary to pulmonary decompensation and shock due to cardiovascular collapse precede death. Almost invariably, fetal death occurs before maternal death. If maternal demise occurs, it does so most commonly about the fourth day following the prodromal illness, and within 24–48 hours after the onset of the clinical features of pneumonia.

Physical examination during the clinical course reveals diffuse bilateral crepitant basilar inspiratory rales. The chest roentgenograms correlate closely with the physical findings. Characteristically, there are diffuse, fluffy bilateral infiltrates radiating from the hilum to the peripheral portion of the lung fields. These infiltrates are not uncommonly sparse. Gram-stained sputum smears are noteworthy in that they fail to demonstrate significant numbers of pathogenic bacteria. At necropsy the lungs are heavy, bulky, and plum-colored. Numerous subpleural hemorrhages are discernible. These changes are most pronounced in the lower lobes. The cut surface of the lung reveals blood-stained frothy fluid as well as hemorrhage both in bronchi and in the lung parenchyma. The microscopic features are characteristic, with widespread necrosis of the tracheobronchial

epithelium as low as the respiratory bronchioles and alveolar ducts. Similar cytopathologic effects are observable within alveolar macrophages. Scattered foci of interstitial mononuclear cell infiltrate can be identified. Intraalveolar hemorrhage secondary to capillary disruption is characteristic. Rare capillary thrombi and hyaline membranes lining the intra-alveolar surface are also present.

Influenza-associated bacterial pneumonia

Purulent sputum, shaking chills, or pleuritic chest pain frequently indicate superimposed bacterial infection. Although the symptoms of pure viral pneumonia may blend directly with and be indistinguishable from those of secondary bacterial pneumonia, in certain instances a short period of improvement intervenes. In the absence of bacteremia the recognition of secondary bacterial pneumonia depends on the identification of bacterial pathogens in Gram-stained sputum. Roentgenographic findings in these two entities may mimic each other exactly; however, pleural effusion, lobar consolidation, or cavitation within the involved lung strongly suggest superimposed bacterial pneumonia.

DIAGNOSIS

The diagnosis of influenzal pneumonia is usually presumptive and is based on a characteristic pattern of disease or roentgenograms occurring at a time when influenzal infection is prevalent in the community. Although it is possible to isolate the virus on the chorioallantoic membrane of embryonated eggs or in a variety of tissue culture lines, the time required for a positive identification and the relative non-availability of isolation systems in most laboratories severely limits its applicability except for necropsy material. Infection can be retrospectively documented by hemagglutination inhibition (HAI) testing utilizing strain-specific viral antigen. A greater than eight-fold rise in the HAI titer (performed by the microtechnique) between acute and convalescent serums is deemed diagnostic of infection with influenza virus.

MANAGEMENT

The frequent inability to distinguish between the two entities dictates a common therapeutic approach. Once the diagnosis of severe influenzal pneumonia is made, the patient should be hospitalized, with appropriate precautions made to isolate her from potential antibiotic-resistant strains of bacterial pathogens indigenous to the hospital environment.

Baseline blood gas values should be obtained. Clinical amelioration or deterioration can be monitored by serial determinations of blood pH, PCO_2, and O_2 saturation. A contracted intravascular space should be anticipated and intravenous therapy should be directed at restoring the intravascular volume, replacing the insensible water loss due to hyperventilation and hyperthermia, and maintaining electrolyte balance. Aggressive intravenous therapy necessitates careful monitoring of the intravascular compartment by a central venous catheter. Should vascular overload occur, rapid but cautious

digitalization is indicated. Marked hypoxia increases the probability of an adverse drug reaction as a consequence of digitalization. The development of shock may require large intravenous doses of corticosteroids.

Vigorous pulmonary therapy includes administration of oxygen and intermittent positive pressure breathing. Progressive deterioration as indicated by blood gas studies may necessitate intubation. Therapy at this point should be performed by specialists.

Operative intervention with evacuation of the uterus, rather than contributing to clinical amelioration, appears to be associated with significantly increased maternal mortality. Because many of the medications used for inducing analgesia or anesthesia may have adverse effects on pulmonary function, it is imperative to involve the anesthesiologist early in the disease. In general, the pregnancy becomes of secondary consideration, and the patient is treated for acute pulmonary decompensation.

Staphylococcal pneumonia is now recognized as the prime bacterial complication in fatal cases of influenzal pneumonia. However, a high incidence of disease due to *Streptococcus pneumoniae* is to be anticipated. *Escherichia coli* is the next most frequent pathogen observed. The spectrum of antibiotic therapy instituted for presumptive bacterial superinfection (nafcillin and gentamicin) should encompass these three major pathogens. The possibility of intrahospital epidemics has focused on the desirability of restricting hospital visits by relatives and friends.

MATERNAL RISK DUE TO PREGNANCY

Without a massive epidemiologic study, it is not established how much added risk influenza imposes on pregnancy. Fragmentary data and anecdotal experience suggest that pregnant women may be at greater risk.

In the 1918 and 1957–1958 epidemics, many pregnant women were among those who developed severe and rapidly fatal pneumonia. In analyzing maternal mortality in these situations, investigators found that most pregnant women died of influenza pneumonia rather than of secondary bacterial infection. In the 1957–1958 epidemic, influenza pneumonia was the leading cause of maternal death in Minnesota. Again, the women died of viral pneumonia and not of a superimposed bacterial infection. After describing a case of fatal maternal influenza in the third trimester, one author stated: “Pregnant women are at increased risk when infected with influenza virus… Perhaps prior vaccination would have averted the disaster.”

Only two deaths were reported as a direct consequence of the 1979 swine flu outbreak: one a military recruit who reputedly left sick bay and ran to catch up to his unit, the other a pregnant 17-year-old with no underlying disease. Figures on morbidity and pregnancy are elusive, but assessment of mortality is not difficult. What is notable about pregnant women is that they die of pure viral pneumonia rather than bacterial superinfection. The only other groups who consistently die of pure viral pneumonia are those with mitral stenosis and chronic bronchopulmonary disease.

Table 17.1 CDC recommendations for influenza vaccination

Annual vaccination is strongly suggested:
(1) For women who will be in the second or third trimester of pregnancy during the influenza season.
(2) For women over the age of 64 years.
Conditions predisposing to such increased risk include:
(1) Acquired or congenital heart disease with actual or potential alterations in circulatory dynamics (e.g., mitral stenosis, congestive heart failure, or pulmonary-vascular overload).
(2) Any chronic disorder or condition that compromises pulmonary function (e.g. chronic obstructive pulmonary disease, bronchiectasis, heavy smoking, tuberculosis, severe asthma, cystic fibrosis, neuromuscular and orthopedic disorders with impaired ventilation, broncho-pulmonary dysplasia following neonatal respiratory distress syndrome).
(3) Chronic renal disease with azotemia or nephrotic syndrome.
(4) Diabetes mellitus or other metabolic diseases.
(5) Severe chronic anemia, such as sickle cell disease.
(6) Conditions that compromise the immune mechanism, including certain malignancies and immunosuppressive therapy.

POSSIBLE FETAL CONSEQUENCES

Stanwell-Smith *et al.* looked at the possible association of influenza infection with fetal or perinatal mortality. They conducted an epidemiological investigation which focused on a small cluster of early and late fetal deaths in early 1986. Women whose pregnancies were affected (cases) were compared with women whose pregnancies had a normal outcome (controls). Case pregnancies were distinguished by a significant excess of recent flu-like illness (p=0.006), and were significantly more likely than controls to have serological evidence of influenza A infection (p=0.00067), predominantly the influenza A H3N2, Christ church/4/85-like strain. The cluster was recognized because most cases were patients of one health center. Larger epidemiological studies will be needed to confirm an association between influenza A and fetal death, but this cluster suggests that influenza A may have an adverse influence on fetal survival.

In a limited number of animal model systems, influenza A virus appears to have some teratogen abilities. Weak circumstantial evidence has been advanced which purports a linkage between maternal infection in pregnancy and a number of late manifesting neurological defects or childhood leukemia.

All know viral teratogens function either by direct cytopathic effect or by indirect inhibition of DNA replication. Except for a case reported by Yawn *et al.*, there is no added data which documents the ability of the influenza viruses to traverse the placental barrier.

VACCINATION IN PREGNANCY

The Centers for Disease Control (CDC) have designated women who are in the second or third trimester of pregnancy during the influenza season as individuals at increased risk for complication and hence a vaccine target population (Table 17.1). Should a pregnant woman have a chronic metabolic disease such as diabetes mellitus, significant renal dysfunction, hemoglobinopathies, chronic disorders of the pulmonary or cardiovascular system or be immunosuppressed, including drug-induced immunosuppression or human immunodeficiency infection/disease, these conditions constitute additive risk factors.

In addition, women who are healthcare workers and other individuals in close contact with persons at high risk should be vaccinated to decrease the risk for transmitting infection to persons at risk.

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or other vaccine components. Influenza vaccine contains three strains, two type A and one type B, representing the influenza viruses likely to be circulating in the United States during the upcoming winter. Different manufacturers may use additional compounds as a preservative such as thimerosal, a mercury-containing compound, or they may use an antibiotic to prevent bacterial contamination. Before administering a vaccine, the package insert should be consulted and vaccine recipient questioned as to known allergies.

The effectiveness of an influenza vaccine is a function primarily of the recipient's age, immunocompetence and the degree of similarity between viruses in the vaccine and those in circulation. When the vaccine and circulating viruses are antigenically similar, influenza vaccine is 70–90% effective. immunity declines in the year following vaccination.

A 0.5 ml dose of either the whole- or split-virus vaccine administered intramuscularly is recommended for women. Immunogenicity and side effects of whole and split-virus vaccines are similar among adults when administered at the recommended dosages. Little or no improvement in antibody response is observed when a second dose of the vaccine is administered in the same season.

Both local and systemic side effects occur. Soreness at the site of vaccination is common and may last up to two days. Fever, malaise, and myalgia tend to occur in individuals with little prior exposure to the viral antigens in the vaccine. Immediate allergic reactions are rare.

CHEMOPROPHYLAXIS

Antiviral drugs for influenza are an adjunct to the vaccine. Four influenza antiviral drugs have been licensed for use in the United States: amantadine, rimantadine, zanamivir and oseltamivir.

Amantadine and rimantadine are chemically related antiviral drugs with activity against influenza A, but not influenza B. They interfere with the influenza virus life cycle. Both are approved for the treatment and prophylaxis of influenza A virus infection. When administered prophylactically to healthy adults before and throughout the epidemic

period, they are 70–90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses.

Zanamivir and oseltamivir are neuraminidase inhibitors with activity against both influenza A and B viruses. Both are approved for the treatment of uncomplicated influenza infections. Only oseltamivir is approved for prophylaxis, but both drugs appear to afford similar effectiveness in preventing febrile illness in community-based studies.

Antiviral agents taken prophylactically can prevent illness but not subclinical infection. Individuals taking these drugs, if infected, will develop immune responses that may protect them when they are exposed to antigenically related viruses in later years. The recommended daily dosage of influenzal medications for treatment and prophylaxis are listed in Table 17.2.

Chemoprophylaxis can be considered for persons with immune deficiency in whom a less than optimal response to vaccination is anticipated. Such patients should be closely monitored for adverse drug reactions, if chemoprophylaxis is administered.

Chemoprophylaxis should not be used in lieu of vaccinations. Antiviral therapy is indicated for nonvaccinated individuals after an outbreak of influenza A has begun in the community. Individuals in this situation should still be vaccinated.

The development of antibodies takes 8–14 days, hence the rationale for concomitant chemoprophylaxis during an influenza outbreak for high-risk women. Amantadine and rimantadine do not interfere with antibody response to the vaccine. When inactivated influenza A virus vaccine is unavailable or contraindicated, amantadine may be administered for up to 90 days in cases of epidemic exposure. Amantadine must be taken each day for the duration of the epidemic or until active immunity has an opportunity to develop after vaccination.

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir or oseltamivir for pregnant women. Both amantadine and rimantadine have been demonstrated to be teratogenic and embryotoxic in animal studies when administered in very high doses. Because of the unknown effects of these drugs on the developing fetus, all anti-influenza virus drugs should be used during pregnancy only when benefits justify the potential risk to the embryo or fetus. These drugs are secreted into breast milk.

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week despite continued drug ingestion.

Table 17.2 Recommended daily dosage of antiviral medications for treatments and prophylaxis

Antiviral agent	*13–64 years*	*≥65 years*
Amantadine[1]		
Treatment	100 mg twice daily	≤100 mg/day
Prophylaxis	100 mg twice daily	≤100 mg/day
Rimantadine[2]		
Treatment[3]	100 mg twice daily	100 or 200 mg/day[4]

Prophylaxis	100 mg twice daily	100 or 200 mg/day[4]
Zanamivir[5,6]		
Treatment	10 mg twice daily	10 mg twice daily
Oseltamivir		
Treatment[7]	75 mg twice daily	75 mg twice daily
Prophylaxis	75 mg/day	75 mg/day

[1]The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 ml/min/1.73m^2
[2]A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 ml/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.
[3]Only approved treatment among adults.
[4]Elderly residents of nursing homes should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged≥65 years of age if they experience side effects when taking 200 mg/day.
[5]Zanamivir is administered via inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of the device.
[6]Zanamivir is not approved for prophylaxis.
[7]A reduction in the dose of oseltamivir is recommended for persons with creatininte clearance <30 ml/min.
Adapted from CDC *MMWR*, 2001; 50:24

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18
Measles

Measles virus is a paramyxovirus. Its virions have a diameter of 100 to 250 nm and consist of a helical ribonucleoprotein core surrounded by a lipid envelope. The virions replicate predominantly in the cytoplasm and are released from the cell surface by budding. The envelope of the virion is composed of at least two glycoproteins: F, which causes membrane fusion and is crucial for infectivity; and H, which is the hemagglutinin. Antibodies to F glycoprotein inhibit viral infectivity.

Measles is an extremely infectious disease entity. The virus is disseminated predominantly by droplet transmission from an infected individual to a susceptible subject in close proximity. Transmission by articles soiled by respiratory secretions may occur. Though any mucosal surface potentially provides a portal of entry, the principal portal of infection is the upper respiratory tract.

The usual incubation period between initiation of infection and onset of the first symptoms (prodrome) is approximately 10 days. Approximately 10 to 14 day intervals between exposure and exanthema occur in 80% of individuals, 15 to 19 days in 14%, and less than 10 days in 6%.

Measles is most communicable during the prodrome and catarrhal stage of infection rather than during the period of the exanthema. Individuals with measles should be considered infectious from the onset of the prodrome (about 4 days before the appearance of the exanthema) until 3 days after the onset of the exanthema. The risk of contagion abruptly diminishes 48 hours after the rash appears. Measles virus is readily recovered from respiratory secretions from 2 days before until 1 or 2 days after the onset of the rash.

Before licensing of live measles vaccine, the incidence of measles in pregnancy ranged from 0.4 to 0.6 cases of measles per 10000 pregnancies. The decline in the incidence of measles associated with the widespread use of the vaccine has further decreased this low incidence of measles in pregnant women. Over half of these cases which now occur are believed to result from primary vaccine failure rather than secondary vaccine failure due to loss of immunity to measles after vaccination. At present, there is no evidence that immunity induced by measles wanes with time.

CLINICAL MANIFESTATIONS

The prodrome typically begins 10 to 11 days after exposure, with fever and malaise, followed within 24 hours by coryza, sneezing, conjunctivitis and cough. During the next 2 to 3 days, this catarrhal phase is accentuated with markedly infected conjunctivae and photophobia. Toward the end of the prodrome, Koplik’s spots appear. These are tiny (no larger than a pinhead), granular, slightly raised, white lesions surrounded by a halo of erythema.

The rash, which appears 12 to 14 days after exposure, begins on the head and neck, especially behind the ears and on the forehead. At first the lesions are red macules 1 to 2 mm in diameter, but during a period of 2 or 3 days they enlarge, becoming maculopapules of 1 cm or greater. By the second day, the exanthema has spread to the trunk and upper extremities. The lower extremities are involved by the third day. The lesions are most prominent in those regions where the exanthema appears first, namely, the face and upper trunk. By the third or fourth day the exanthema begins to fade in the order of its appearance. A brown staining of the lesions often persists for 7 to 10 days and is followed by fine desquamation.

The clinical course of measles can be greatly altered by administration of immune globulin (IG) during the incubation period. In modified measles, the catarrhal phase may be completely suppressed and the exanthema limited to a few macules on the trunk.

Table 18.1 Adverse fetal consequences of maternal rubeola (measles) in pregnancy

Abortion*
Fetal death *in utero**
Congenital infection

*Fetal wastage is probably as contingent upon the severity of maternal disease as on the gestational age of the fetus.

The principal complications associated with measles are pneumonia, encephalitis, and myocarditis. Encephalitis occurs in one per 10000 cases of measles. Measles encephalitis has a mortality rate approaching 10%. Liver enzyme elevations may occur in 50–75% of young adults. It is not uncommon for adults with arrested tuberculosis to have an acute flare-up following measles.

MEASLES IN PREGNANCY

The incidence of death and other complications from measles during pregnancy may be higher than expected for age-comparable, non-pregnant women (Table 18.1). Pneumonia which is a relatively rare complication in the general population is increased in pregnancy.

Eberhart-Phillips *et al.* identified 58 gravida with measles. Thirty-five, 60%, were hospitalized for measles, fifteen, 26%, were diagnosed with pneumonia, and two, 3%, died of measles complications.

In Packer's series of cases, six of eighteen pregnant women with measles were said to suffer from 'severe' disease. Christensen *et al.* describe an epidemic of measles in Greenland. Pregnant women were nearly three times as likely to die from their infections as nonpregnant women with measles aged 15 to 54. In a hospital based study of women in Houston, seven had pneumonia and one died.

PERINATAL WASTAGE

Measles in pregnancy may lead to high rates of fetal loss and prematurity, especially within the first two weeks after onset of the rash. In Eberhart-Phillips' series and excluding three induced abortions, eighteen pregnancies, 31 %, ended prematurely; five were spontaneous abortions; and thirteen were preterm deliveries. All but two of the eighteen pregnancies that terminated early did so within 14 days after onset of the rash. Two term infants were born with minor congenital anomalies, but their mothers had measles late in their third trimester.

CONGENITAL MEASLES

Because the usual incubation period from infection to the first appearance of the exanthema is 13 to 14 days, measles exanthemas acquired in the first 10 days of life are considered transplacental in origin, whereas those appearing at 14 days or later are probably postnatally acquired.

By-and-large, the outcome of gestational measles on the fetus is relatively benign. The spectrum of disease in congenital measles varies from a mild illness in which a rash and Koplik's spots may or may not be present to fulminating fetal disease in which pneumonia is the leading complication. Mortality, if it occurs, tends to do so in a premature infant. The case fatality ratio is not well established and is probably significantly influenced by the gestational age and maternal/fetal immune response. Administration of IG at birth may decrease the mortality. The dose usually administered has been 0.25 mg/kg.

Overt neonatal disease usually is seen when maternal disease occurs in the periparturitional period.

Disease in the newborn is not associated with enhanced virulence or an expanded pattern of disease. There is no evidence to incriminate the measles virus as a teratogen for the human fetus.

Neonatal disease is usually but not invariably at the same stage of development as that of the mother. Most of the progeny of pregnancies which have been complicated by maternal measures exhibit apparent immunity when subsequently exposed to rubeola virus.

Most women of childbearing age in urban areas are immune to measles because of previous natural infection or vaccination. Because it is amply documented that infants born to immune mothers are usually protected by transplacentally acquired antibodies, measles outbreaks in newborn nurseries are extraordinarily rare events.

DIAGNOSIS

Maternal

A definitive diagnosis of maternal measles can be inferred on purely clinical grounds when there is history of recent exposure and the typical catarrhal phase is followed by

Koplik's spots and a maculopapular exanthema in the characteristic distribution. Koplik's spots are deemed to be pathognomonic.

More characteristically, the clinical impression is confirmed by serological testing. For routine determinations of antibodies in paired human sera, the hemagglutination inhibition (HI) test is faster, less cumbersome and less expensive than the neutralization or enzyme-linked immunofiltration assay (ELISA) test. For detecting antibodies after infection in the remote past or for predicting immunity, the neutralization test is somewhat more sensitive. Recent maternal infection can be inferred by the demonstration of IgM anti-measles antibodies in the ELISA test system. Serum antibodies appear shortly after the appearance of the rash and peak in three to four weeks. Definitive diagnosis of rubeola is contingent on demonstration of IgM-specific antibodies, a four-fold or greater rise in paired sera run in the same test or isolation of the virus.

The measles virus is best isolated using primary cultures of human embryonic kidney or rhesus monkey kidney. Presumptive isolates of measles virus are identified by typing with known antiserum in hemadsorption inhibition or plaque reduction tests.

Congenital

The diagnosis of congenital measles is contingent upon the disease process being present at birth or developing in the first twelve days of life and either recovery of virus or the demonstration of specific IgM or IgA virus antibodies in neonatal blood.

THERAPY AND PREVENTION

Management of maternal myxovirus infection is largely supportive in terms of symptomatology. If hyperthermia develops, fever must be aggressively controlled. Antibiotics are indicated if pulmonary secondary bacterial superinfection occurs.

MANAGEMENT OF THE EXPOSED GRAVIDA

Mothers with an unequivocal history of either previous natural measles or vaccination with live attenuated measles virus are assumed not to be at risk when exposed to measles in the neonatal period. If a mother without a history of previous measles or measles vaccination is exposed 6 to 15 days antepartum, she may be in the incubation period and capable of transmitting measles infection during the postpartum period. In the absence of a previous maternal history of measles, the neonate should remain in the newborn nursery.

Both mother and the neonate should receive IG, 0.25 mg/kg intramuscularly, to prevent or modify subsequent measles infection that might have been incubating at the time of delivery If exposed less than 6 days antepartum, she would not be capable of transmitting measles by the respiratory route until at least 72 hours postpartum.

PROPHYLAXIS

In the absence of prior vaccination or immunity, the administration of gamma globulin during the incubation period for any individual with HI titers of less than 1:2 is indicated. This level of antibody is highly correlated with susceptibility to measles.

Immune globulin prophylaxis given within 72 hours of exposure prevents infection in the majority of instances. Efficacy diminishes linearly with time. Some protection may exist as long as 6 days after initial exposure. The recommended dose of IG is 0.25 ml/kg IM, not to exceed 15 ml. IG given after this period before the prodrome usually results in modification of the measles infection with diminished morbidity

Those non-immune gravidae, if well beyond the first 3–4 weeks of pregnancy, given IG prophylaxis should be considered for vaccination if the disease persists in the general population. An interval of at least 8, and preferably 12, weeks should be allowed to pass so that residual measles antibodies do not interfere with a vaccine ‘take’.

All infants born to mothers with active measles in the six days before delivery also should receive IG.

MEASLES VACCINE

Measles vaccine is a live-attenuated virus vaccine that produces a mild or inapparent non-communicable infection. A single subcutaneously administered dose of live measles vaccine provides durable protection against measles illness for 95% of susceptible individuals.

Non-pregnant adults who are exposed to measles and who have no or uncertain documentation of live measles vaccination on or after their first birthday, no record of physician-diagnosed measles, and no laboratory evidence of immunity should be vaccinated within 72 hours after exposure; vaccination is most likely to be protective during that time. If the exposure did not result in infection, the vaccine should induce protection against subsequent measles infection.

An acceptable alternative is to use IG, which can prevent or modify infection if administered within 6 days after exposure. This alternative is principally indicated when measles vaccine is contraindicated. IG should not be used in an attempt to control measles outbreaks.

Vaccine adverse reactions

A temperature of >103ºF (39.4ºC) may develop among approximately 5–15% of vaccinees, usually beginning between the fifth and twelfth days after vaccination; fever usually lasts 1–2 days and, rarely, up to 5 days.

Rashes have been reported among approximately 5% of vaccinees. Encephalitis after measles vaccination is extremely rare, and its incidence cannot be discerned from the background incidence of encephalitis of an unknown etiology. The incidence of postvaccination encephalitis is much lower than the incidence after natural measles.

Vaccine precautions

Vaccination should not be postponed because of a minor illness, such as a mild upper respiratory infection. However, vaccination of persons with severe febrile illnesses should be postponed until recovery. Vaccine should be given 14 days before—or deferred for at least 6 weeks and preferably 3 months after—a person has received IG, whole blood, or other blood products containing antibody.

Persons with a history of any sign or symptom of an anaphylactic reaction (e.g. hives, swelling of the mouth and throat, difficulty breathing, hypotension or shock) after ingestion of eggs or receipt of neomycin should be given measles vaccine only with extreme caution. Protocols have been developed for vaccinating such persons.

Persons with reactions that are not anaphylactic are not at increased risk and can be vaccinated. Because of a theoretical risk to the developing fetus, measles vaccine should not be given to pregnant women.

The vaccine also should not be given to persons who are immunocompromised as a result of immune deficiency diseases, leukemia, lymphoma, or generalized malignancy or who are immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, orradiation.

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19
Mumps

Mumps virus, like measles virus, is also a member of the paramyxovirus family. The mumps virus contain a hemagglutinin neuraminidase glycoprotein or viral (V) antigen associated with the envelope, a hemolysis cell fusion (F) glycoprotein antigen also associated with the envelope, and a soluble (S) antigen associated with the ribonucleoprotein core.

The mumps virus is transmitted primarily by droplet, saliva and fomites. The initial site of virus replication is the upper respiratory tract from which a viremia is engendered which results in metastatic glandular and central nervous system involvement.

Mumps is an acute, generalized, communicable disease whose most distinctive feature is swelling of one or both parotid glands. Involvement of other salivary glands, the meninges, the pancreas and the testes of postpubertal males occurs with some frequency.

The usual incubation period, between exposure to infection and onset of parotitis is 14 to 18 days. The extremes between 7 and 23 days have been identified.

The prodrome consists of fever, malaise and myalgia. Parotitis, if it is to develop, does so in the next 24 hours. Parotid gland involvement progresses for two to three days and then gradually regresses.

MUMPS IN PREGNANCY

When mumps is superimposed on pregnancy, the resultant disease is not appreciably more severe than it is in non-pregnant women. In general, the clinical course of mumps in pregnancy is relatively benign. Mumps virus has been isolated from breast milk.

PERINATAL WASTAGE

Like measles, mumps infection when superimposed upon pregnancy may adversely affect its outcome. Small studies have demonstrated a greater than two-fold increase in perinatal wastage. Mumps differs from measles in the sense that some studies have identified an increased incidence in congenital defects as well as abortions; however, in the largest series involving 501 cases, no significant difference in terms of fetal complications could be demonstrated between gravida whose pregnancy had been complicated by mumps and the control group, irrespective of the stage of pregnancy at which infection occurred. Unlike fetal deaths or abortions associated with measles, those associated with mumps are closely related temporally to the maternal infection.

CONGENITAL INFECTION

In extremely rare incidences maternal mumps has produced congenital disease. The infants present with parotitis at birth or develop it in the ensuing ten days of life. In general, the disease tends to pursue an uneventful course. Occasionally severe systemic involvement is noted. Lacour *et al.* reported a case in which the mother developed bilateral parotitis beginning the day of the delivery. The child was subsequently severely ill and suffered from fever, splenomegaly and thrombocytopenia, however without partotitis or pancreatic involvement. Both mother and child recovered with symptomatic treatment. When maternal disease occurs in the immediate periparturitional periods, the neonate may develop parotitis or aseptic meningitis.

MUMPS EMBRYOPATHY

The prime controversy concerning maternal mumps during gestation centers around the question of whether there is a mumps embryopathy. Retrospective studies have noted a higher incidence of delayed hypersensitivity to mumps in infants with endocardial fibroelastosis than in the control groups. This observation has not been universally substantiated. Despite the ability of mumps virus to induce congenital malformations in experimental animals, there is no definite evidence of teratogenicity for mumps virus in humans.

There is question as to whether maternal disease in gestation is causally related to childhood onset diabetes mellitus. Fine *et al.* conducted a long term follow up study of 3076 subjects who were exposed to viral infection *in utero* and who at the time of analysis were up to 40 years of age. Mortality and morbidity were compared with those in a control population matched for sex and date and area of birth. There was evidence of an increased risk of diabetes among those exposed to mumps during the first trimester (four cases among 128 subjects against none of 148 controls).

DIAGNOSIS

The diagnosis of mumps is not problematical on clinical grounds when bilateral, painful parotitis develops especially when a history of recent exposure is available. The virus can be recovered from saliva or urine by cultivation on a variety of cell tissue culture lines. Definite diagnosis requires either serological confirmation, virus isolation or specific documentation using polymerase chain reaction (PCR).

Serologically, the diagnosis of mumps is established by demonstrating a rising antibody titer in paired acute and convalescent sera. Complement fixation, hemagglutination inhibition and neutralization tests can demonstrate seroconversion to mumps V antigen. These test systems have largely been replaced by the introduction of highly sensitive enzyme-linked immunosorbent assay (ELISA) tests which are capable of identifying both IgG and IgM anti-mumps antibodies. Measurement of IgM mumps antibodies can also be measured using a variation of the ELISA known as antibody capture.

THERAPY

Treatment is largely symptomatic. Application of cold packs to the parotid glands in conjunction with the liberal use of analgesics may be beneficial. If mastitis develops, application of cold packs can be used. Mumps vaccine may be used to immunize serosusceptible individuals in the home or hospital environment. Mumps vaccine is not recommended for pregnant women. Immunoglobulin is of little value in aborting mumps or its complications.

MUMPS VACCINE

A single dose of live mumps vaccine administered subcutaneously provides protective and long-lasting levels of antibody. Clinical vaccine efficacy reports range between 75% and 95%. Recurrent disease does occur. Mumps outbreaks have been reported in highly vaccinated populations. These occurrences have brought into advocacy the use of two doses of MMR vaccine.

VACCINE INDICATIONS

Mumps vaccine is indicated for all adults believed to be susceptible. Persons should be considered susceptible to mumps unless they have documentation of physician-diagnosed mumps, adequate immunization with live mumps vaccine on or after their first birthday, or laboratory evidence of immunity. Most adults born before 1957 are likely to have been infected naturally and can be considered immune, even if they did not have clinically recognizable mumps disease.

VACCINE ADVERSE REACTIONS

Parotitis and fever after vaccination have been reported rarely. Allergic reactions including rash, pruritus, and purpura have been associated temporally with mumps vaccination but are uncommon, usually mild, and of brief duration. The frequency of reported central nervous system (CNS) dysfunction after mumps vaccination is not greater than the observed background incidence rate in the general population.

VACCINE PRECAUTIONS

Because of the theoretical risk of fetal harm after administration of a live-virus vaccine to a pregnant woman, avoiding administering mumps vaccine to pregnant women is prudent.

Mumps vaccine should not be given to persons who are immunocompromised as a result of immune deficiency diseases, leukemia, lymphoma, or generalized malignancy or

to persons who are immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

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20
Rubella

Clinical rubella was first described in Germany by De Bergen in 1752 and Orlow in 1758. Considered sort of a ‘bastard measles’, it was given several names, the principal ones being Rotheln, rubeola, and German measles. The latter name was engendered by the early interest of these German investigators.

In 1886, Veale formally proposed the name rubella for the disease.

“The name of a disease is always a matter of importance. It should be short for the sake of convenience in writing, and euphonious for ease in pronunciation. It should not be a question-begging appellative. Rotheln is harsh and foreign to our ears, rubeola notha and Rosalia idiopathica are too long for general use, and are certainly expressive of conclusions which have yet to be proved. I therefore venture to propose Rubella as a substitute for Rotheln.”

During the early 1970s, most cases of rubella occurred in children and young adolescents. By 1999, adults accounted for 86% of cases. Seventy-three percent of individuals with rubella were Hispanic. Most of these persons were foreign-born. Recent outbreaks of rubella occurred in individuals from Mexico and Central America.

The rash characteristic of rubella virus is a maculopapular eruption. It usually begins on the upper thorax or face and spreads in a wavelike pattern to involve first the thorax then the abdomen, and finally the extremities over approximately a 3-day period. It is not uncommon for the rash to be fully developed on the lower extremities at the same time that there is early fading of the rash around the face and neck. Characteristically, the rash lasts for 3 days; hence its popular name ‘the 3 day measles’, as contrasted to that of rubeola, the 7 day measles’.

Arthralgia (and occasional instances of arthritis) is not an uncommon complication in adults, particularly young women. Depending on the strain virulence of the virus, the incidence of clinically significant arthralgia may approach 20%.

Not all viral infections associated with an exanthema of 3 days’ duration are rubella. Exanthemas comparable to that observed with rubella infection have been described with echovirus and coxsackie virus infections and type A hepatitis. The diagnosis of rubella can be inferred on clinical grounds by the additional finding of postauricular adenopathy. The postauricular adenopathy may be detectable 6–7 days prior to the onset of rash and persists for 1–2 weeks after its disappearance.

CONGENITAL RUBELLA FOLLOWING MATERNAL INFECTION

The aggressive use of childhood and strategic vaccination programs have dramatically reduce the incidence of congenital rubella cases. During 1997–1999, a total of 21/26 of

congenital rubella cases occurred in Hispanic infants. Most of the mothers were foreign-born.

The probability of involvement of the developing fetus by rubella virus is in part a function of when in gestation maternal infection occurs. An inverse relationship exists between clinical manifestations of the teratogenic potential of rubella virus and the age of the embryo at the time of maternal infection within the first 90 days of pregnancy. The earlier in development maternal infection occurs, the greater the probability of significant fetal involvement. In light of the augmented knowledge concerning congenital rubella, it is apparent that there are no adequate statistics that can translate the true incidence of infection *in utero* into a problematic figure. Nevertheless, certain principles are evident:

(1) The further advanced the pregnancy is from the tenth week, the less the probability of overt fetal involvement. If congenital involvement occurs,

Table 20.1 Probability of fetal involvement following maternal infection in gestation

Month of maternal infection	***Probability of overt congenital rubella***	***Probability of congenital rubella***
First	50%	The inability to quote a precise probability of involvement is due to a number of factors: 1. The 'normal'appearing infants, who harbor rubella virus in their biological fluids, are readily missed when only clinical parameters are used to calculate the incidence of involvement.
Second	25%	2. Many of the symptoms are not detectable early in life, i.e. in two separate studies only 50% of the malformations presented signs or symptoms at birth. In another study, while deafness was detected in 6% of the infants at 2 years of age, it was found in 13% of the same group at 3 years of age.
Third	10%	
Fourth	1–2%	3. The mother can contract subclinical rubella.

fetal involvement is more likely to result in an incomplete form or forme fruste of the syndrome rather than the full-blown congenital rubella syndrome.

(2) Even within the period of maximum susceptibility to the teratogenic effect of the virus, although the incidence of involvement of the fetus *per se* is markedly increased, it is nonetheless a random phenomenon. Gestational age is just one of the many variables for fetal involvement.

Based on epidemiologic data, the chances of having an infant with congenital rubella syndrome as a consequence of maternal infection in the first trimester are estimated to be between 18% and 20% (Table 20.1). Although statistics are an adequate reflection of the teratogenicity of rubella virus, they fail to delineate the total morbidity resulting from congenital infection. Formes frustes of rubella embryopathy due to continuous virus-cell interaction ('the expanded congenital rubella syndrome') have gone unrecognized. Once

it was recognized that infection of the fetus could still result in normal-appearing neonates, it became apparent that the incidence of transplacental infection could not be monitored from clinically overt disease alone. Involvement of the fetus and the persistence of viral infection into the first year of life meant that delayed morbidity was to be anticipated because of continued virus-cell interaction during somatic growth. Previous statistical assessments of the possibility of fetal involvement as opposed to teratogenicity were invalid, owing to their failure to include congenital rubella infants without overt rubella syndrome or formes frustes.

Only fragmentary data exist which might shed some light on the true incidence of congenital infection as well as its translation into morbidity and mortality. The effect of the 1964 epidemic in Baltimore on the outcome of pregnancy was studied prospectively in 1086 women enrolled in a prenatal program at Johns Hopkins Medical Center. When maternal infection occurred in the first trimester, 4 of the 7 live-born infants had defects compatible with rubella syndrome; 6 of the 7 were small for their age. The seventh was normal in all clinical aspects tested; however, rubella virus was recovered from the throat washings on two occasions.

Morbidity from congenital rubella is not restricted to maternal infection in the first 90 days. Hardy *et al.* described variants of rubella embryopathy in the progeny of mothers who contracted infection in the early part of the second trimester. They reported on 24 women with clinical and laboratory evidence of rubella between the 14th and 31st weeks of pregnancy. In the two cases of fetal loss, the rubella virus was recovered from the products of conception. Although

Table 20.2 Clinical findings in symptomatic neonates with the ‘expanded’ congenital rubella syndrome

Organ system	***Clinical findings***
Bone	Micrognathia Bony radiolucencies
Cardiovascular system	Pulmonary arterial hypoplasia Patent ductus arteriosus Coarctation of aortic isthmus Interventricular septal defect Interauricular septal defect Myocardial necrosis Myocarditis
Central nervous system	Encephalitis Microcephaly Dystrophic calcification Bulging fontanel Neurologic deficits Progressive panencephalitis
Ear	Hearing defects Peripheral Central

Eye	Retinopathy Cataracts Cloudy cornea Glaucoma Microphthalmos
Genitourinary system	Hypospadias Unilateral agenesis Renal artery stenosis with hypertension
Hematopoietic system	Anemia Dermal erythropoiesis (blueberry muffin syndrome) Immunologic dyscrasias Leukopenia Thrombocytopenia with/without purpura
Liver	Hepatitis Hepatosplenomegaly Jaundice (regurgitative)
Lungs	Interstitial pneumonitis (acute, subacute, chronic)
Pancreas	Diabetes mellitus
Growth and development	Growth retardation Intrauterine Extrauterine Prematurity Psychomotor retardation: intellectual, behavioral, autistic, educational difficulties

the 22 live-born infants were incompletely sampled, the virus was isolated from 3 of them. Of the 22 infants, 7 were clinically normal and had no detectable antibody at 6 months of age. Of the remaining 15 infants suspected to be abnormal, 6 had elevated IgM levels and 10 had detectable levels of antibodies after 6 months of age. Although morbidity may occur as a consequence of second-trimester fetal involvement, the incidence of congenital malformations by the fifth month approaches its background norm.

PATHOGENESIS

Following maternal infection in the first trimester, rubella virus is recoverable from the products of conception in up to 64% of cases. If maternal rubella is prospectively confirmed, either by viral isolation or serologic conversion, the incidence of recovery approaches 100%. Involvement of the conceptus is almost invariably the result of hematogenous dissemination associated with maternal viremia. Involvement of the conceptus takes one of the two principal forms, either:

(1) recovery of virus is limited to the placenta; or
(2) there is concomitant widespread organ involvement.

It is this latter pattern of viral infection which correlates with congenital rubella. Once infection of a given organ system is achieved, virus replication may continue throughout gestation and well into the first year of life.

Despite widespread organ involvement, the teratogenic manifestations of rubella virus are primarily limited to those organ systems with a limited capacity to regenerate (Table 20.2). Certain facets of rubella embryopathy require not only the establishment of infection within that organ system, but also its involvement at a critical phase of organogenesis. As with drug-induced embryopathy, vulnerability of the developing fetus is partly a function of time, wherein minimal insult, either direct, in the form of virus-cell interaction resulting in necrobiosis, or indirect, in the form of inhibition of mitosis, can have an exaggerated effect. Both of these possibilities are functional postulates in the pathogenesis of congenital rubella (Figure 20.1).

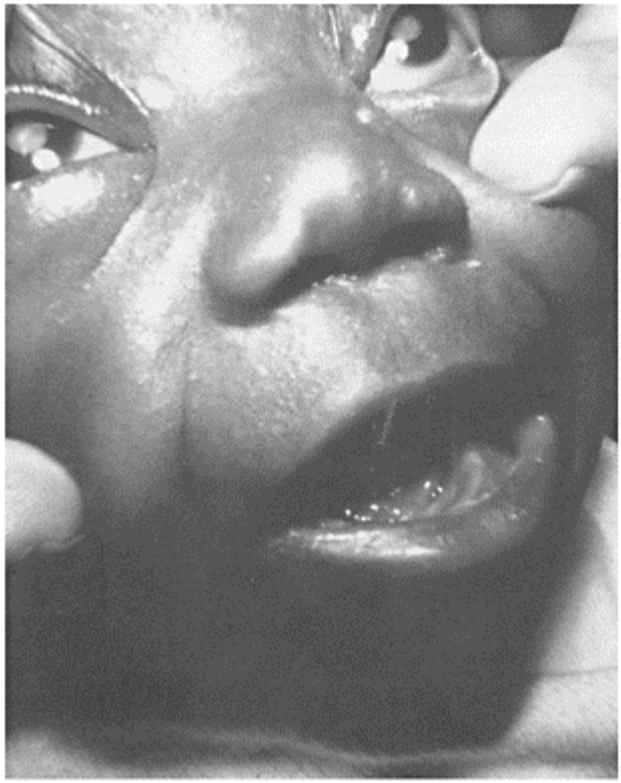

Figure 20.1 Bilateral congenital cataracts which, with cardiovascular, central nervous system, and inner ear abnormalities, constitute the so-called classic stigmata of congenital rubella.

An inverse relationship exists between manifestations of the teratogenic potential of rubella virus and gestational age within the first 90 days of life. This may be a partial function of alterations in placental structure during early growth and development or the loss of the complementary viral receptor sites on cell surfaces.

Even when fetal infection has occurred within the first 90 days of gestation, in rare instances the infants, although possessing virus in all their biologic fluids except blood, have been deemed normal by every clinical parameter. In these instances, the effects of rubella virus have been either negligible or offset by the limited regenerative capacity of those tissues which are compromised in the classic rubella syndrome.

Virus persistence and continued virus-cell interaction during *in utero* existence is responsible for a wide spectrum of clinical disease in the neonatal period. Thrombocytopenia, hemolytic anemia with extramedullary hematopoiesis, hepatitis, interstitial pneumonitis, myocarditis, myocardiopathy, interstitial nephritis, encephalitis, interstitial pancreatitis, and osteomyelitis have all been observed in infants with congenital rubella (Table 20.2). These manifestations of cellular dysfunction and necrobiosis have prompted the use of the term ‘the expanded congenital rubella syndrome’.

Infants with congenital rubella develop a neurologic syndrome, progressive rubella panencephalitis, during the second decade of life. The progressive neurologic deterioration observed is characterized by motor spasticity, ataxia, intellectual deterioration, and seizures. Examination of the cerebrospinal fluid (CSF) reveals elevated protein and gamma-globulin levels, in conjunction with a high rubella antibody titer in both the serum and the CSF. Rubella virus has been isolated from the brain biopsy of one such patient.

POSTNATAL PERSISTENCE

The postnatal persistence of rubella virus is one of the major enigmas in our understanding of the pathogenesis of rubella embryopathy. Acquisition of rubella infection in the neonatal period or later results in a limited period of virus replication within internal organ systems and at free epithelial surfaces. Thirty days after the onset of rash there is no evidence of continued virus replication, a finding that is in sharp contrast to the condition as it exists in an infant with congenital rubella. Once the fetus is infected *in utero*, virus replication persists throughout gestation. Approximately 90% of all neonates with congenital rubella syndrome have virus in most of their extravascular biologic fluids, such as CSF, urine, tears, and swabbings of the conjunctiva and posterior part of the oropharynx.

The earliest postulate advanced to account for viral persistence was immune paralysis, namely, that the fetus exposed to an antigen in appropriate quantity *in utero* would be rendered incapable of synthesizing specific antibodies to the antigen. Congenital rubella furnished an exciting model system in which infection could antedate implantation.

Analysis of the serum of infants with congenital rubella shows it to contain a composite of specific IgG and IgM antibodies. Because IgM of maternal origin is excluded from the fetal circulation, this finding constituted presumptive evidence of congenital infection. At age 34 months, infants with congenital rubella do not exhibit

significant absence of neutralizing or hemagglutination-inhibition antibodies, as would be anticipated if the titers were totally contingent on transplacentally acquired maternal immunoglobulins.

That the IgM antibodies are functional is suggested by the infrequency of recovery of rubella virus from the serum of neonates in the neonatal and postnatal periods, as opposed to its recovery from multiple organs. Having said this, one must focus on what perhaps is the critical issue in congenital infection. The response of host to virus is not that of a single, but of a dual, biologic system in which the maternal host is capable of a more accelerated response than the fetus. The fetus at the time of immunologic competence is involved in antigenic processing and initial antibody synthesis. The maternal host has already responded to infection and is now flooding the fetal compartment with a high titer of specific antibody. What is the influence of specific maternal IgG antibody on the immune response?

It has been clearly demonstrated, either *in vivo or in vitro*, in multiple animal systems, and in man, that exogenous administration of specific antibody may suppress *in vivo* endogenous production of antibody to that immunogen. The best example of this is probably the use of Rho(D) human immune globulin to prevent sensitization of an Rh-negative woman. The function of specific antibody is postulated to result in the destruction of immunologically committed lymphocytes. The possibility that this phenomenon functions in fetuses has been suggested by three sets of observations:

(1) There is a prolonged phase of IgM antibody synthesis in congenital rubella as opposed to that in neonatally acquired infection. In the latter, the conversion from the IgM to the IgG antibody response occurs 6–20 weeks prior to that observed in congenital rubella.
(2) Some 10% of infants with congenital rubella exhibit dysgammaglobulinemia or hypogammaglobulinemia. The characteristic pattern is an elevated IgM level with a low IgG level and absence of IgA. Eventually, there is a re-emergence of the IgG and IgA classes of immunoglobulins.
(3) Some infants with documented congenital rubella fail to produce specific antibodies to rubella virus in the first two years of life.

Having touched on the conversion from specific IgM to IgG, we can now see the ramifications. A total of 80% of IgM is maintained within the intravascular space as contrasted to 20% at the interstitial sites of virus replication. With the conversion, the interstitial distribution of immunoglobulins is markedly altered so that a threefold increase in specific antibody is achieved at the interstitial site of replication (60% of IgG is extravascular). Marked similarity exists between the curves of apparent immune elimination of the virus and the emergence of specific IgG. The correlation is not absolute for a given case. Although the shift in the type of immunoglobulin synthesis is probably of great importance in the ultimate nonrecovery of virus, other factors function concomitantly. Otherwise, a tighter correlation between the two phenomena would be anticipated.

Many investigators have explored the possibility that chronic rubella viral infection may be the result of defective cellular immunity. Although decreased delayed hypersensitivity can be demonstrated in infants with congenital rubella, it is not unlike that observed in normal individuals during acute viral infection and following

administration of viral vaccines. While delayed hypersensitivity plays a prominent role in certain facets of the histopathology of congenital rubella, it has yet to be demonstrated that chronic viral infection is primarily the result of defective cellular immunity.

Clinical significance of persistence

Approximately 50% of infants with congenital rubella will have recoverable virus in their biologic fluids at six months of age. Rubella virus has been recovered from lens fragments as long as three years following birth.

The persistence of rubella virus has very pragmatic ramifications. Infants with congenital rubella are a source of infection among nurses and are responsible for the 'second generation' congenitally malformed infants in pregnant females caring for these children. Consequently prophylactic measures need to be instituted to guard the immediate paramedical and medical personnel within the delivery suite and on the obstetric ward.

The inability to supply prospective identification of all potentially infected infants, owing to inapparent maternal illness or the lack of maternal participation in a prenatal program, should prompt the screening of all potential vectors within the nursing and medical community. It is not enough to merely determine the antibody status of the women who are currently pregnant or may soon become so. A susceptible nurse may become infected and may serve as a vector in disseminating infection among a young childbearing population. Though the diagnosis of congenital rubella may be made after parturition, it is often recognized within the incubation period of rubella virus. Thus, prospective knowledge of the susceptibility of the nursing staff permits both:

(1) the assessment of the probability of the subsequent development of infection among personnel exposed to the infant, the amniotic fluid, or the placenta; and
(2) initiation of proper quarantine.

DIAGNOSIS

Congenital

Laboratory diagnosis of congenital rubella infection only requires any one of the following:

(1) Demonstration of a rubella-specific IgM antibody or infant IgG rubella antibody level that persists at a higher level and for a longer time than expected from passive transfer of maternal antibody (i.e. rubella titer that does not drop at the expected rate of a twofold dilution per month). Approximately 20% of infected infants tested for rubella IgM might have detectable titers before age one month. Infant with symptoms consistent with congenital rubella who tested negative soon after birth should be retested at age one month.
(2) Isolation of rubella can be obtained from nasal, blood, throat, urine, or cerebrospinal fluid specimens. The best results are from throat swabs. An infant with congenital

rubella syndrome should be considered infectious until two cultures of clinical specimens obtained one month apart are negative for rubella virus.

(3) Detection of virus by reverse transcription and polymerase chain reaction methodology (RT-PCR). This process can be used to detect the presence of rubella virus after growth in tissue culture or directly in clinical specimens.

RT-PCR has been used to document rubella placentitis; however demonstration of rubella virus in the placenta correlates poorly with secondary dissemination to the fetus.

Maternal

A clinical case of adult rubella is defined as an illness characterized by (1) acute onset of a generalized maculopapular rash; (2) temperature greater than 37.2ºC (99.0ºF) and (3) arthralgia/arthritis, lymphadenopathy (usually suboccipital, postauricular and cervical); or conjunctivitis.

Maternal rubella is most commonly documented serologically with the demonstration of a greater than eightfold rise in the specific antibody titer obtained from specimens drawn on or before the rash and 7–10 days following its clinical appearance.

Not infrequently, the obstetrician or gynecologist is confronted with a gravida who had a rash 3 or 4 days earlier. Paired serologic specimens obtained within the first 5 days following may still demonstrate possible serologic conversion (rubella infection). When more than five days have elapsed since the onset of a rash, the presence of postauricular adenopathy in conjunction with a high rubella titer containing specific IgM antibodies can substantiate the diagnosis of recent infection. Rubella IgM antibodies appear one week after the onset of infection and persist for approximately one month. To document recent maternal infection with rubella virus, the IgM ELISA test should be utilized.

EXPOSURE TO RUBELLA DURING GESTATION

One of the most common problems of clinical management is that of a gravida with known exposure to rubella virus. At the time of the initial visit it is imperative to obtain a sample of serum for testing. Since antibodies first appear at the time of the rash, any significant titer of specific antibody prior to the presumed onset of rash or possible subclinical illness (days 11 through 17) is indicative of prior infection. A gravida with pre-existing antibody can be reassured about the safety of her fetus in terms of the potentially deleterious effects of rubella virus. Absence of specific antibody indicates susceptibility. The patient is given an appointment to return in 18–20 days or at the time of clinical symptoms (fever, malaise, arthralgia, and rash), whichever comes first. At the time of this follow-up visit, the patient is carefully re-evaluated for postauricular adenopathy (Figure 20.2). Approximately 25–30% of maternal infections can be expected to be subclinical. Although rash may not develop, postauricular adenopathy not infrequently does. Postauricular adenopathy, even in the absence of rash, should arouse a high index of suspicion of infection with rubella virus. Definitive diagnosis is contingent on the demonstration of an eight-fold increase in specific antibody titer. An eight-fold increase in the convalescent specimen drawn 21–24 days after exposure, or 7–10 days after the onset of the rash, serologically confirms the diagnosis. Serologic evaluation at

the time of the rash is still valid, since the peak antibody titers will not be reached for another 7–10 days.

There is no place for gamma-globulin in the clinical management. Administration of specific antirubella antibodies can only suppress the clinical manifestation of rubella and the appearance of endogenous specific antibody. If gamma-globulin has been given to susceptible individuals following intimate exposure to rubella virus, serologic surveillance must be extended for at least another 30 days. In the experimental model systems, the concomitant administration of exogenous specific antibody with an immunogen results in partial suppression or ablation of the immune response.

Once a case of rubella is confirmed, the appropriate health agencies must be immediately notified. Even one documented case needs to be treated as a potential outbreak. Since 30–50% cases of rubella infection are subclinical, investigation of an apparent isolated case may reveal the occurrence of additional cases.

VACCINATION OF WOMEN OF CHILDBEARING AGE

The vaccination strategy adopted by the United States in 1969, the year rubella vaccine was licensed, was aimed at controlling rubella in preschool and young school-aged children, the known reservoirs for rubella transmission. The intention was to thereby prevent exposure of susceptible adolescents and young adults, especially women. By 1977, vaccination of children 12 months of age and older had resulted in marked declines in reported rubella incidence in children and had interrupted the characteristic 6- to 9-year rubella epidemic cycle; however, this vaccination strategy had less effect on rubella incidence in persons 15 and over (i.e. childbearing age for women). Approximately 10–20% of this latter population continued to be susceptible, a proportion similar to that of prevaccine years. Most importantly, reported endemic congenital rubella syndrome had continued at a low but constant level. When this problem was recognized, public health authorities targeted other groups for vaccination. Increased efforts were made to vaccinate junior and senior high school students, enforce rubella immunization requirements for school entry and for all susceptible military recruits, and recommend vaccination of pregnant women. The incidence of congenital rubella syndrome has been significantly reduced. The advent of rubella vaccines has markedly altered the natural history of congenital rubella and, in so doing, has delineated new responsibilities for the discipline of obstetrics and gynecology namely vaccination of women of childbearing age.

It is recommended for these groups that they should receive the vaccine only if they are shown to be susceptible to serological testing, and if they agree to prevent pregnancy for two months after immunization. Furthermore, programs undertaking prenatal or antenatal screening for

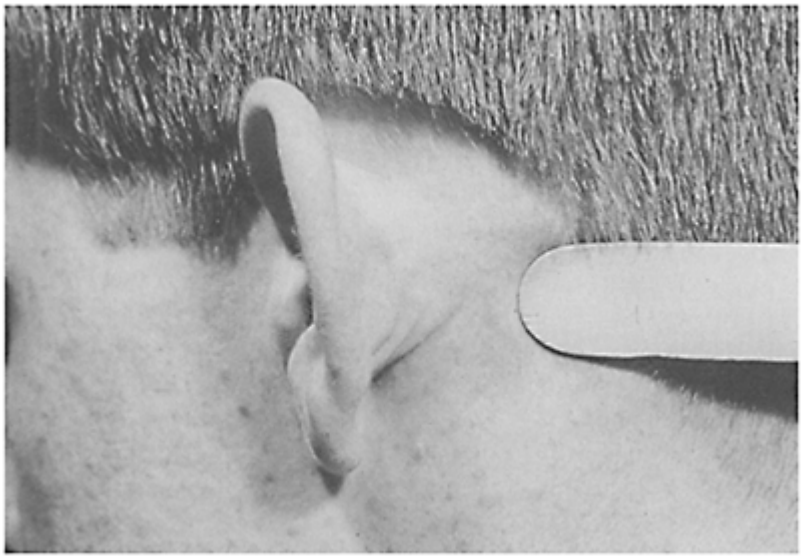

Figure 20.2 Postauricular adenopathy associated with rubella virus infection

rubella susceptibility and, if appropriate, immunization in the postpartum period, need to be developed if the critical population, women of child-bearing age, are to be effectively protected from the possibility of giving birth to a child with rubella embryopathy.

The major impediment to the vaccination of women of childbearing age is the recognition that vaccine strains of rubella virus can, in rare instances, reach the products of conception. That intrauterine rubella infection may follow immunization of the gravida underscores the need for careful selection and monitoring of the population to be vaccinated. Prior to vaccination, the criteria that must be met include documented susceptibility, absence of pregnancy, and demonstration of a reliable form of contraception. An HA1 antibody titer of 1:10 or less usually indicates susceptibility to infection. However, prior to vaccination the patient should undergo a pregnancy test and should use an effective modus of contraception, which should be continued for three menstrual cycles after vaccination. Noteworthy is the immediate postpartum period as a time for vaccination; also attractive as a situation for vaccination is the family planning clinic.

No congenital rubella syndrome (CRS) defects have been noted when pregnant women have been vaccinated with RA 27/3 vaccine. Rubella vaccine viruses, including the RA 27/3 strain, can cross the placenta and infect the fetus. Approximately 1–2% of infants born to susceptible gravida vaccinated in pregnancy had serologic evidence of subclinical infection, regardless of vaccine strain. On the other hand, while the rubella virus isolation rate from the products of conception for the RA 27/3 vaccine is only 3% (1/34), the rate of virus isolation for Cendehill and HPV-77 vaccines is 20% (17/85). These data indicate that the risk of placental or fetal infection from RA 27/3 vaccine is

minimal. In view of the data collected through 1985, the Immunization Practices Advisory Committee (ACIP) continues to state that:

(1) pregnancy remains a contraindication to rubella vaccination because of the theoretical albeit small risk of CRS;
(2) reasonable precautions should be taken to preclude vaccination of pregnant women, including asking women if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others; and
(3) if vaccination does occur within three months before or after conception, the risk of CRS is so small as to be negligible; thus, rubella vaccination of a pregnant woman should not ordinarily be a reason to consider interruption of pregnancy. The patient and her physician, however, should make the final decision.

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21
Varicella-zoster virus (chickenpox)

Varicella-zoster virus (VZV) is a member of the herpesvirus family. The mature particle is approximately 1800 A in diameter and consists of a linear double-stranded DNA molecule center core surrounded by an icosahedral capsid and a lipid envelope. The capsid is composed of 162 elongated hexagonal prisms, called capsomeres.

The outer envelope is derived from the inner nuclear membrane of the host cell. Having a significant phospholipid component, it is sensitive to both ether and chloroform degradation. The site of biosynthesis of viral DNA is the nucleus of the whole cell. Even though the site of assembly of viral particles is cytoplasmic as well as nuclear, virus replication within a cell produces an eosinophilic intranuclear inclusion body.

VARICELLA (CHICKENPOX)

The average incubation period is 11 days; the range is from 10 to 21 days. With direct parenteral inoculation, disease may develop in as few as nine days. Fever is usually the first sign of illness. Within a day, a maculopapular rash appears on the skin and mucous membranes. The lesions rapidly undergo vesiculation and appear as superficial thin-walled vesicles which appear in crops and are intensely pruritic. All stages from maculopapular to encrusted lesions can be observed simultaneously This pattern distinguishes varicella from variola (smallpox), in which all the lesions are synchronous. The patient's temperature is in the range 101º-103ºF. Varicella-zoster virus usually can be obtained from vesicular fluid but rarely from other sites. Individuals with varicella should be considered to be infectious from 24–48 hours before to five days following the appearance of the first vesicles when the scabs have become dried. The infectivity period of herpes zoster is about the same as for varicella.

HERPES ZOSTER

Herpes zoster represents an immunological modification of latent chickenpox. After the patient recovers from varicella, the virus persists in a latent form within the peripheral nervous system. The triggering mechanism for reactivation of viral synthesis is poorly understood. Its clinical manifestation is shingles, in which the cutaneous lesions, rather than being generalized, are restricted to one to three dermatomes. Because of the sensorineural ganglion involvement, intense pain is characteristic of this manifestation of the VZV.

Varicella is uncommon in the first three months of life. The transplacental transfer of maternal antibody appears to be able to modify clinical expression of postnatally acquired

varicella zoster infection such that the infant develops zoster rather than chickenpox. The factors responsible for preventing the activation of latent varicella-zoster virus are unknown. Although it is postulated that serum antibody is the critical determinant, evidence is accumulating that cell-mediated immunity may be a more important factor. The risk of developing herpes zoster appears to be augmented in immunosuppressed patients and patients with Hodgkin's disease who have lost their cell-mediated responses. Varicella occurs more frequently during the late winter and early spring. Since herpes zoster is not caused by exogenous reinfection, it occurs with equal frequency throughout the year. The incidence of herpes zoster increases with age, whereas most cases of varicella occur in children.

VARICELLA AND PREGNANCY

Varicella superimposed upon pregnancy causes three distinct sets of problems:

(1) enhanced maternal morbidity and mortality;
(2) adverse impact *in utero* on organogenesis and growth; and
(3) potentially lethal parturitional disease in the neonate.

Maternal morbidity and mortality

Greater than 90% of children have serological evidence of varicella-zoster before they reach adolescence or adulthood. The incidence of chickenpox among women of childbearing age is under 5%. The attack rate in pregnancy is between one to two cases per 10000 pregnancies. These figures are probably conservative estimates owing to the under-reporting of mild cases.

Varicella, when it occurs in an adult, tends to be more severe than in preadolescence. While the incidence of chickenpox is no higher in pregnant than in nonpregnant women, in pregnant women in advanced stages of gestation, infection is more likely to run a complicated course, with possible development of pneumonia, encephalitis, hepatitis, pancreatitis, and/or nephritis.

MATERNAL EXPOSURE TO VARICELLA

Inquiry should be made as to prior history of varicella or zoster. Barring gross alterations of the patient's immune state, prior disease confers life-long immunity. If the patient is uncertain about prior diseases and one or more family members cannot confirm its occurrence, a serological test to determine immune status should be performed. Maternal virus specific IgG antibody levels as determined by enzyme-linked immunosorbent assay (ELISA) or the fluorescent antibody test for membrane antigen can be done. If exposure was beyond the standard incubation period for varicella-zoster by more than five days, and if maternal IgG antibody is detected, the serum specimen should be retested to determine whether IgM specific antibodies are concomitantly present. If IgM antibodies are demonstrated, a second serum sample should be tested five to seven days later. The

presence of IgM antibodies are indicative of recent infection. The presence of IgM specific antibodies and a greater than fourfold rise in titer of a pair specimens in parallel is diagnostic of acute infection.

If acute maternal infection or seronegativity (with the risk of continued intimate exposure) is documented, the patient can be offered varicella-zoster immune globulin (VZIG). The usual dose of VZIG is 125 units per 10 kg body weight, administered intramuscularly, up to a maximum of 625 units (five vials). The cost of VZIG varies between $100 and $600. While reasonably effective in preventing or attenuating varicella if given within 4 days of exposure, the value of VZIG in the presence of acute disease is not well established.

VARICELLA-ZOSTER (CHICKENPOX) PNEUMONIA IN PREGNANCY

Much speculation exists as to whether varicella in pregnancy is complicated by an increased incidence of pneumonitis. The incidence of pneumonia in adults is probably about 16%. In a review of 173 cases of varicella complicated by pneumonia, Harris and Rhoades found 30 deaths, or a mortality rate of 17%. Of the 17 cases of varicella pneumonia complicating pregnancy, 7 terminated in maternal deaths, giving a mortality rate of 41%.

Most cases of varicella pneumonia in pregnancy have occurred in the third trimester at a time when it has been demonstrated that maternal cell-mediated immunity is depressed.

Respiratory symptoms usually develop when the cutaneous lesions have been present from 2 to 5 days (Figure 21.1). The initial sign is a dry, non-productive cough. In many instances this may be the sole manifestation of pulmonary involvement, and no symptomatic progression beyond this stage may be noted. In those patients with more severe disease, the cough, after 36–48 hours, becomes productive of a mucoid sputum, which may become blood-streaked; frank hemoptysis can occur. Dyspnea, tachypnea, and cyanosis may subsequently develop. Chest pain indicates parenchymal disease extending to the pleural surface. Symptoms may

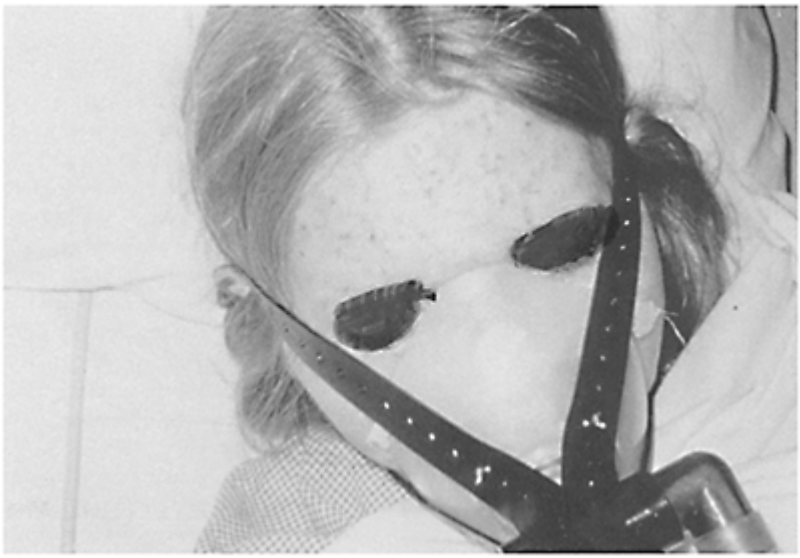

Figure 21.1 Varicella pneumonia complicating gestation in the third trimester. Oxygen saturation measurements on room air were as low as 57%. Following her recovery, the patient delivered at term a normal healthy infant

progress with frightening rapidity. Physical examination usually reveals minimal abnormal findings despite extensive roentgenographic evidence of pulmonary parenchymal involvement. The X-ray films characteristically reveal a widespread bilateral acinonodular infiltrate. The nodular densities seem to be superimposed on markedly increased bronchovascular markings. The infiltrates are most accentuated in the hilar regions, and while apices may be relatively spared, no areas are completely free of disease. In moderately severe cases, the respiratory symptoms may persist for 7–10 days.

The sudden increase in tachypnea and tachycardia may be signs of impending cardiovascular collapse. Clinicians must be aware of the insidious nature of the disease and of the gross disparity between initial relatively mild symptoms and potentially fulminating lethal disease.

Varicella pneumonia is but the clinical manifestation of disseminating disease. If sought for, evidence can be occasionally demonstrated for multiple organ involvement (pericarditis, myocarditis, hepatitis, pancreatitis, encephalitis).

The pathologic process is primarily an extensive mononuclear cell infiltration of the interstitium, with focal areas of coagulative necrosis associated with alveolitis. Septal cells may become cuboidal and form multinucleated giant cells. Within septal cells or

macrophages, the characteristic intranuclear inclusion body of the VZV may be identified.

The National Institutes of Health study group has recently identified two maternal risk factors. Women who are smokers and women with extensive cutaneous lesions (100 or more lesions) who contract varicella during pregnancy are at greater risk for developing the pneumonic complications.

Diagnosis

The differential diagnosis is usually not in doubt in view of the characteristic cutaneous and pulmonary findings, and the frequent history of chickenpox in progeny or household contacts. Laboratory analyses are not particularly helpful. The white blood cell count tends to be normal or slightly elevated, with a shift to the left, and the Gram smear of the sputum is unremarkable. The definite diagnosis of varicella-zoster infection resides in either serologic confirmation or virus isolation.

Therapy

Supportive therapy is comparable to that utilized in influenzal pneumonia. Salient features of management include the following:

(1) Administration of oxygen, primarily via a positive pressure apparatus. This is often helpful in relieving the dyspnea.
(2) Intravenous maintenance of fluids and electrolyte balance. As a rule, patients with varicella-zoster pneumonia tend to have intravascular hypovolemia.
(3) If central venous pressure rises, digitalization of the patient before acute pulmonary edema occurs.
(4) With significant hemoptysis, especially in a patient with pre-existing anemia, transfusion therapy with concomitant digitalization.
(5) Obtaining serial sputum smears and cultures, and antibiotics, if secondary bacterial infection is suspected.

It a pregnant woman develops VZV, antiviral therapy is indicated to prevent severe and life-threatening complications. In the United States, acyclovir has been approved for the treatment of acute VZV.

Acyclovir has been used in gravida with varicella pneumonia in the late second and third trimester. Most case reports involve the use of intravenous acyclovir 5 to 18 mg/kg every 8 hours for 5 to 10 days. Pulmonary function improved in most women with therapy, but one patient died after increasing pulmonary dysfunction.

Smego *et al.* retrospectively evaluated the use of acyclovir in 21 women with varicella pneumonia in their second or third trimester of pregnancy. Sixteen of the women were previously reported in the literature and five of the women were newly reported by the investigator. Those women received a short course of oral acyclovir 600 to 800 mg four to five times daily for five days following intravenous therapy. Due to pneumonia, ventilatory assistance was required in 5 of twelve women in their second trimester and in 7 of 9 women in their third trimester. Deaths associated with uncontrolled infection or complications occurred in 2 of 21 (14%) women. Among the women who died, two of

the three infants born also died. One infant was stillborn and one infant was born prematurely. Women at highest risk for fatality were those in their third trimester of pregnancy who required mechanical ventilation. Preliminary evidence suggests that acyclovir is safe and the drug is safe for the developing fetus when given during the last trimester.

The antiviral drugs, acyclovir, valacyclovir and famciclovir have been approved for treating herpes zoster.

Some physicians have used oral valacyclovir, one gram three time a day for 7 to 10 days in the therapy of acute VZV in pregnancy.

Huang *et al.* have shown that the combination of intravenous immunoglobulin (IVIG) and acyclovir intravenously administered 7 days after the onset of maternal rash can effectively prevent perinatal varicella.

IVIG should be offered to pregnant, varicella-seronegative women with significant exposure to vzv.

The patient who develops varicella pneumonia near term may require hospitalization. To counteract possible nosocomial spread, respiratory isolation with dressing precautions should be instituted. This means a private room with the door closed at all times; use of masks, gloves, and gowns; restricting equipment to use only in that room (an article possibly contaminated by direct contact or secretions must be handled as infectious and disposed of properly); handwashing upon leaving the room; and restricting personnel who care for the patient to those with a history of prior varicella or those over the age of 30 and not pregnant.

FETAL WASTAGE

Postpartum goals are focused clearly on the neonate and on maximizing its well-being. The possibility of congenital involvement, that is, the occurrence of disease at birth or before the tenth day of life, must be assessed. In those cases in which maternal disease occurs immediately prior to the delivery, strict isolation must be instituted.

In general, maternal infection with the VZV during the first trimester does not result in a detectable increase in fetal wastage unless associated with severe maternal illness.

Abortion may ensue in those instances complicated by varicella pneumonia. Early abortion or prematurity is thought to be secondary to maternal hypoxia and febrile response. The degree of maternal hypoxia can be marked. The interstitial pneumonitis creates an alveolar-capillary block upon which is imposed intraalveolar hemorrhage.

IN UTERO VARICELLA

While the bulk of fetal wastage associated with varicella is the consequence of the severity of the maternal disease, congenital varicella may occur as a result of both clinical and subclinical maternal infection. Congenital varicella is defined as disease occurring in the neonate before the tenth day of life. Maternal and neonatal disease most often are nonsynchronous. This discrepancy in the stage of development of lesions between mother and neonate strongly suggests the possibility that transplacental infection depends on the

second viremia from placental sites. Although most cases of congenital infection in the world literature are varicella, congenital herpes zoster does occur.

Up to 25% of progeny born to gravidae whose pregnancies were complicated by varicella will have serological evidence of congenital infection, however the incidence of overt congenital anomalities ranges from 0% to 9%. The best test for predicting morbidity as opposed to infection is ultrasonography. Ultrasound findings suggestive of congenital varicella include ventriculomegaly, microcephaly, limb abnormalities, intrauterine growth retardation and dysmorphic calcification in multiple organs, especially the liver.

There is little evidence to suggest that subclinical infection modifies the ability of the virus to establish infection *in utero*. Varicella rarely has an incubation period shorter than 10 days. Congenital varicella is defined as (1) a disease occurring before the tenth day of life or (2) the characteristic syndrome of developmental anomalies associated with maternal chickenpox in the first 15 days of life or (3) presence of IgM or IgA specific antibodies at birth.

Transplacental transmission of VZV is not limited by gestational age nor the severity of maternal disease. Varicella-zoster virus is not recoverable in the neonates whose mothers had chickenpox in the first trimester despite morphological and serological evidence of *in utero* infection or disease. The most probable consequence of second trimester and early third trimester congenital varicella-zoster is complete resolution *in utero*. In an unpublished prospective study by Ann Arvins of 43 pregnant women whose gestations were complicated by maternal varicella, eight of the 43 resultant progeny demonstrated immunologic evidence of *in vitro* infection. Only one of these eight neonates had viral-induced anomalies. This baby was one of 11 neonates born to mothers who contracted their disease in the first trimester.

VARICELLA-ZOSTER EMBRYOPATHY

The time in gestation that varicella occurs markedly influences the pattern of ensuing disease. Chickenpox which occurs early in gestation may be associated with multiple developmental abnormalities (Table 21.1). La Foret and Lynch, in 1947, were the first to describe a syndrome characterized by low birth weight, areas of critical skin scarring (Figure 21.2), hypotrophic limbs (Figure 21.3), eye abnormalities and neonatal growth retardation. The ophthalmologic lesions include microphthalmia, cataracts, optic atrophy and chorioretinitis. The demonstrable neurologic defects include motor and sensory deficits, overt paralysis, and/or dysphagia. Postnatally, such infants may exhibit a failure to thrive. Psychomotor retardation and seizures are not uncommon. Necropsy analysis supports the thesis that the observed embryopathy is the result of viral cytopathic effects which are magnified by incomplete organogenesis.

Sauerbrei *et al.* using polymerase chain reaction (PCR) demonstrated VZV DNA in formalin-food samples of lung, spleen, adrenal glands, bulbus oculi and

Table 21.1 Clinical and laboratory findings in five infants born following maternal varicella in early pregnancy

Findings	*Individual Cases*									
	1	*2*		*3*		*4*		*5*		
Gestational varicella	8 wk	13–14 wk		11 wk		9 wk		13–15 wk		
Low birth weight for gestational age	+	+		+		+		+		
Skin lesions	+	+		+		+		+		
Hypotrophic limb	Right lower	Right lower		Right upper		Left upper		Left lower		
Seizures	+	+		+		–		+		
Cortical atrophy	+	+		+		Not reported		+		
Ophthalmologic observations	Bilateral optical atrophy	Chorioretinitis		Chorioretinitis		Left Horner's syndrome		Microphthalmia, cataracts, chorioretinitis		
Virus isolation	Not reported	Negative		Not reported		Not reported		Negative		
Varicella-zoster antibody titer (complement-fixing)	Not reported	Day 13	Day 63	5 mo	8 mo	6 wk	Day 2	5 mo		
Infant		1:16	1:32	1:32	1:8	1:40	1:256	1:128		
Mother		1:64	1:8	Not reported		1:320	1:128	1:64		

Modified from Srabstein JC, *et al., J Pediatr* 1974; 84:239

placenta from a 34 week old stillborn with hypophthamos, hypoplasia of the extremities and skin lesions.

The full-blown La Foret-Lynch syndrome occurs in neonates whose mothers contracted chickenpox during the first 15 weeks of gestation. The syndrome is not constant. Some neonates exhibit the complete spectrum of pathology whereas others have only one or two organ systems involved.

Congenital VZV infection can occur in the abscence of overt maternal illness. Mustonen *et al.*, in their study of 201 neonates, identified four babies with neurological varicella induced sequelae whose mothers had asymptomatic infection during pregnancy.

PERIPARTURITIONAL VARICELLA

When gravida develop varicella late in the third trimesterwithin 17 days of delivery, 24% of the ensuing progeny will develop overt disease. The incubation period from onset of maternal rash to the onset of rash in the newborn is 11 days (range nine to 15 days). This discrepancy between maternal and neonatal lesions suggests that transplacental infection is dependent on a second viremia from fetal endothelial sites within the placenta and that only occasionally is the congenital form of the disease a consequence of the primary viremia in the maternal host. In rare cases, the primary maternal viremia induces simultaneous disease in both mother and fetus. Middlecamp reported the presence of congenital varicella at birth in fraternal twins whose mother developed the disease on the day prior to delivery. Similarly, Harris reported two cases of congenital varicella in which maternal and neonatal lesions were in a comparable stage of development. With the exception of these four cases, varicella in the mother and in the newborn are nonsynchronous.

Timing of maternal disease is a critical factor for neonatal outcome. When maternal disease has occurred within five days prior to delivery, at five to 10 days of life, the ensuing progeny are prone to develop a severe form of varicella characterized by disseminated intravascular coagulopathy superimposed upon viral pneumonitis and hepatitis. Thirty percent of these neonates die. If the onset of maternal rash is more than five days postpartum and the neonate develops a disease in the first four days of life, the morbidity and mortality are significantly modified by the presence of specific maternally derived antibodies.

The order of appearance and the distribution of the eruptions in the newborn are similar to the pattern seen in adults. The initial lesions appear on the torso

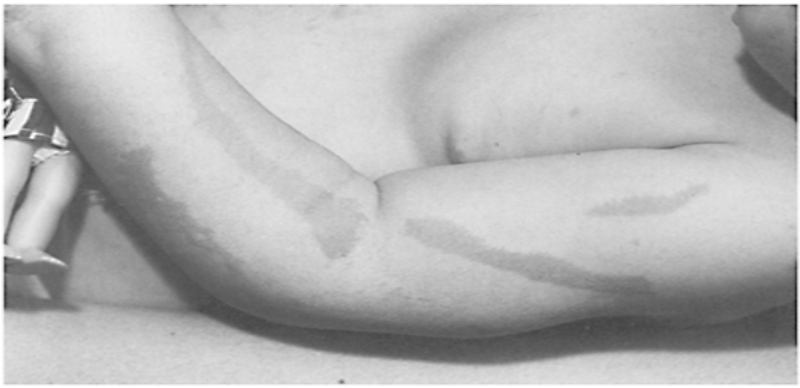

Figure 21.2 Cutaneous scars in a child suspected of having had congenital varicella. (Courtesy of WE Bell, MD, lowa City, IA)

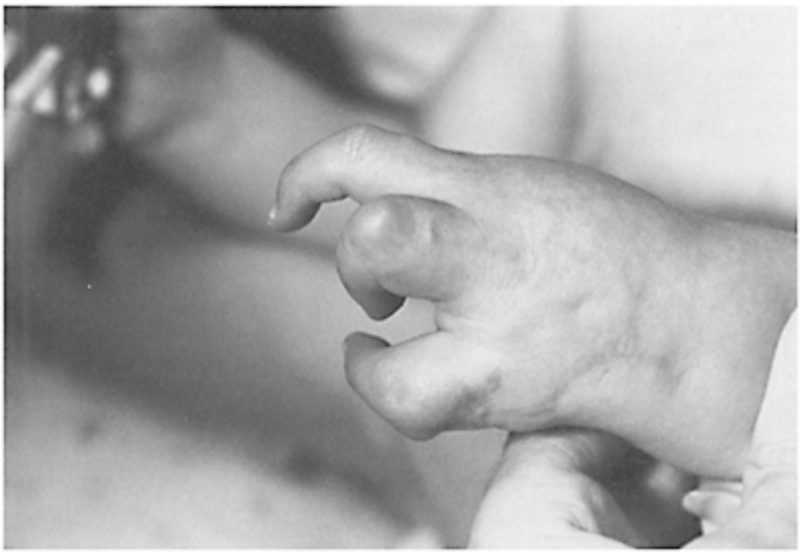

Figure 21.3 Digital anomalies in the same child as in Figure 21.2. (Courtesy of WE Bell, MD, Iowa City, IA)

and then spread centrifugally. Successive crops of lesions develop in such a manner that later in the disease, an infant may exhibit macules, vesicles, and pustules simultaneously. Respiratory difficulty may develop between the second and third day after the initial cutaneous lesions. This time interval between the onset of cutaneous lesions and respiratory distress is comparable to that of varicella pneumonia in the adult. The development of respiratory distress carries with it an ominous prognosis.

The placenta exhibits both gross and microscopic foci of miliary coagulative necrosis. The adjacent intervillous spaces are filled with necrotic material, leukocytes, and nuclear fragments. Some of the villi may exhibit granulomatous lesions in the stroma consisting of areas of necrosis surrounded by epithelioid cells, a few foreign-body giant cells, and mononuclear elements. Some of the decidual cells contain intranuclear inclusion bodies consisting of an eosinophilic central mass surrounded by a clear halo and rimmed by fragments of chromatin along the nuclear membrane.

Fatal cases of congenital and neonatal varicella are indistinguishable on anatomic and histologic grounds. Postmortem examinations have revealed widespread systemic involvement, with characteristic areas of focal necrosis associated with intranuclear inclusion bodies and secondary hemorrhage. The most important lesions involve the lungs. The pulmonary parenchyma exhibits areas of focal necrosis. In some cases, an interstitial pneumonitis may be present. Miliary areas of coagulative necrosis may be identified, involving liver, pancreas, esophagus, stomach, adrenal cortices, thymus, spleen, and bone marrow. At the margins of these lesions, eosinophilic intranuclear inclusion bodies are present in adjacent epithelial cells.

NOSOCOMIAL VARICELLA IN THE NEWBORN NURSERY

Nosocomial spread of varicella is an uncommon event owing to the underlying presence in most neonates of transplacentally acquired specific maternal antibodies. Even when chickenpox occurs (after the 9th day of life) as a result of postnatal nursery exposure, it is usually attenuated. Infants born of mothers who contracted varicella within two weeks prior to delivery should be regarded as potentially incubating the virus. Such infants are best isolated to minimize the possibility of horizontal transmission of infection to other neonates, postpartum mothers or hospital personnel. If the baby does not develop the disease and lacks specific antibodies, it is best to isolate the baby from the mother if she still has evidence of the disease.

NEONATAL HERPES ZOSTER

The fetus may develop an infection with varicellazoster *in utero* which resolves before birth. Such infants harbor the virus which later in life reactivates to cause zoster. This association of maternal chickenpox during gestation and early onset of zoster in the child has been reasonably well documented. Brunnell *et al.* reported a series of cases of zoster in children ranging from three and a half months to two years of age. In each case, the mother had experienced clinically overt varicella during pregnancy. None of these infants had any stigmata of intrauterine varicella-zoster infection at birth. Infants who acquire varicella *in utero* appear to have difficulty in maintaining virus in its latent state. Ordinarily, zoster is a disease of the elderly.

DIAGNOSIS

Maternal disease

A presumptive diagnosis of varicella or herpes zoster is made primarily on the basis of a characteristic pattern of disease. Definitive documentation requires serologic confirmation or virus isolation or demonstration.

Rapid diagnosis of varicella or zoster infection can be done using a fluorescein-conjugated VZV monoclonal antibody test. Cell scrapings obtained from the base of one or more vesicles is smeared onto a glass slide and air-dried. The cells are then probed with the conjugated VZV-specific monoclonal antibody. Vesicular fluid collected with a sterile tuberculin syringe is appropriate material for virus isolation in cell cultures.

Complement-fixing antibodies to the virus are demonstrable four to five days after the onset of the disease and the titer continues to rise for about two weeks. Viral neutralization, immunofluorescent and enzyme-linked immunoassay identification can be used. The availability of such methods for serologic identification, as well as viral isolation, tends to be variable. Demonstration of VZV-specific antibodies during the course of disease similarly documents etiology.

Immunofluorescent or ELISA are reliable tests for documenting prior infection with VZV.

Congenital disease

Congenital varicella is usually defined as varicella occurring in a neonate before the tenth day of life. This definition is based on the shortest incubation period accepted for varicella. The work of Steiner in human volunteers suggests that eight rather than nine days may represent the shortest incubation period for varicella. In those cases in which maternal disease occurred prior to delivery and congenital varicella ensued in the immediate postpartum period, an eight day interim between the two events was not uncommon.

Although the gross and microscopic pathology of varicella embryopathy are sufficiently characteristic to warrant a high index of suspicion as to the probable etiologic agent, the specific incrimination of VZV resides in either the occurrence of classic maternal disease, serologic confirmation of prior specific infection and/or virus isolation.

Immunofluorescent tests have been adapted to detect VZV-specific IgM antibodies.

PROPHYLAXIS AND THERAPY

Maternal

The pruritis can be controlled with local applications of calamine lotion. Systemic antipruritics are rarely required, and until their effects in the fetus are established, it would be wise to avoid their use in pregnant women. The skin should be kept clean by daily bathing to prevent secondary infection. Complications such as pneumonia, encephalitis, myocarditis, hemorrhagic disorders, or nephritis are managed with therapeutic agents directed at the specific problems.

There are no specific guidelines for the management of a pregnant woman who is exposed to or develops varicella early in gestation. Pregnant women with a history of previous chickenpox or prior chickenpox in their immediate progeny are probably not at risk. Varicella-zoster immune globulin is the only apparent potentially therapeutic modality

Some experts have recommended VZIG administration for pregnant women with negative or uncertain prior histories of varicella who are exposed in the first or second trimester to prevent congenital varicella syndrome or in the third trimester to prevent neonatal varicella. However, there is no evidence that administration of VZIG to a susceptible, pregnant woman will prevent viremia, fetal infection, or congenital varicella syndrome. In the absence of evidence that VZIG can prevent congenital varicella syndrome or neonatal varicella, the primary indication for VZIG in pregnant women would be to prevent complications of varicella in a susceptible adult patient rather than to prevent intrauterine infection. VZIG is supplied in vials containing 125 units per vial (volume is approximately 1.25 ml). The recommended dose is 125 units per 10 kg (22 lbs) body weight, up to a maximum of 625 units (i.e., five vials). Fractional doses are not recommended. VZIG has not been evaluated as a prophylactic measure for prevention or attenuation of varicella in normal adults.

VZIG is mandatory 1.25 ml (one vial) IM for all progeny of mothers with onset of rash less than five days.

If VZIG is not available, 1.0–1.5 ml/kg of immune globulin will not prevent but may attenuate disease.

In 1995, the FDA approved a live attenuated VZV vaccine for children. The vaccine is recommended for all non-pregnant susceptible women of childbearing age. Pregnancy should be avoided for three months after vaccination. The vaccination regimen requires two doses one month apart. Protection has been reported to be >94% of immunized persons, vaccine use in pregnancy is contraindicated.

Neonatal

If a neonate is delivered during the incubation period of the mother but before viremia, the risk of neonatal chickenpox is minimal unless the infant is exposed to the virus. The period of greatest risk for severe and potential lethal disease occurs when the infant is born within one day before or four days after the onset of maternal varicella.

The progeny of mothers with onset of rash less than five days prior to parturition should receive VZIG as soon as possible. Zaia *et al.* reported no deaths in 133 neonates who received VZIG in the first 24 hours. Slightly over 50% of the VZIG recipients developed mild disease. The recommended dose of VZIG for the neonate is 1.25 ml (one vial) IM. If VZIG cannot be obtained, high doses of immune serum globulin (1.0–1.5 ml/kg) should be used, although it will probably not prevent infection. The use of intravenous acyclovir, prophylactically and therapeutically, has not been assessed in clinical studies.

Since its licensure on February 1, 1981, VZIG has been produced and distributed in Massachusetts by the Massachuetts Public Health Biologic Laboratories (MPHBL) and distributed elsewhere by the American Red Cross Services- Northeast Region through regional blood centers.

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22
Calymmatobacterium granulomatis

Granuloma inguinale was first recognized in 1882 by McLeod who named it serpiginous ulcerations of the groin. In 1905, Colonel Donovan described the intracellular, rodshaped bodies known since as Donovan bodies.

The ultrastructure of *Calymmatobacterium granulomatis* in human tissue is typical of Gram-negative bacteria. *C. granulomatis* appears to share antigenic determinants with various members of the *Klebsiella* genus. Because of the antigenic similarities and the requirement for a low oxidation-reduction potential, the organism was initially postulated to be a member of the Enterobacteriaceae. A distinguishing feature is the large capsule around the bacterium within mononuclear cells. The demonstration of phage material within *C. granulomatis* has suggested the possibility that *C. granulomatis* is a phage-modified bacterium. Phage modification may be the necessary prerequisite to translate fecal bacterial contamination into the disease state.

The determinants of disease and the factors responsible for the pathogenic expression of this organism are poorly understood. Although disease can be produced with some regularity with infected human material, as a rule organisms grown on appropriate culture media fail to produce infection when inoculated into human volunteers.

It has been postulated that *C. granulomatis* is primarily a constituent of the gastrointestinal tract which is auto-inoculated from the rectum into sites of both sexual and non-sexual trauma. Poor personal hygiene is thought to be a contributing factor. Disease is usually endemic in areas with both high temperatures and humidity. In the United States, disease occurs primarily in port cities in the southern part of the United States.

The disease is apparently not very contagious. While a significant mode of transmission involves sexual contact, the disease does not invariably affect conjugal partners despite repeated contact.

NATURAL HISTORY OF THE DISEASE

Donovanosis is a chronic, progressive ulcerative disease involving primarily the genital region. The predilection of lesions for the genital areas and the occasional occurrence of disease in sexual partners of infected individuals constitute the prime evidence to support the concept of granuloma inguinale as a venereal disease.

The prevalence of the disease among pederasts and the predominant anal and perianal predilection of the lesions strongly suggest that rectal coitus is the prime means of transmission of infection, either by contamination of the skin directly through anal intercourse (whether it be heterosexual or homosexual) or indirectly by faulty hygiene. Further evidence supporting the inferred thesis of venereal disease transfer, secondary to

rectal coitus, can be drawn from the observations that the disease process is infrequent among prostitutes. In the preantibiotic era, individuals in the florid stage of the disease only occasionally transmitted infection to their sexual partners. From clinical studies, an incubation period of 17.4 days has been calculated; however, experimental infection of human volunteers has produced disease in 50 days.

The disease is only mildly contagious. In most cases lesions cannot be demonstrated in sexual consorts. Evidence of infection as opposed to disease is detected in 12–52% of marital or steady sexual partners.

The common sites for lesions, in women, are the labia minora, fourchette, and labia majora. The perianal region also can be affected. Bedi has reported an unusual case of non-venereal transmission of perianal granuloma inguinale in a child. Another site that may occasionally be affected by this disease is the oral cavity.

Clinically the disease presents as painless, progressive ulcerative lesions without regional lymphadenopathy. The initial lesion usually begins as a reddish-brown, flat-topped papule which often spreads and then ulcerates in the center. Not infrequently, other papules appear at about the same time. When they ulcerate, the lesions eventually coalesce.

The ulcer may show variation in its morphology:

(1) the ulcerative or ulcerogranulomatous form—the fleshy, exuberant lesion—presents as a beefy-red granulomatous ulcer, usually single, which is nontender, non-indurated, and bleeds profusely on touch (owing to its high vascularity);
(2) the hypertrophic or verrucous form consists of an ulcer or growth with a raised, irregular edge or surface, drier than the ulcerative variety, with an elevated, granulomatous base;
(3) the necrotic type gives rise to extensive destruction of genitalia with profuse, foul-smelling exudate; and
(4) the sclerotic or cicatricial variety presents as a band-like scar in and around the genitalia.

As a rule, the ulcer tends to have a clean base composed of fresh granulation tissue and to have well-defined borders. The advancing edge of the lesion exhibits a scrolled appearance owing to epithelial hyperplasia and acanthosis of the squamous epithelium (Figure 22.1). The degree of hyperplasia (and not infrequently dysplasia) in response to infection may cause an erroneous diagnosis of low-grade squamous cell carcinoma. The lesion or lesions may develop secondary bacterial infection or may be co-infected with another sexually transmitted pathogen.

Spread of the disease may be by contiguous contact, autoinoculation, or lymphatic extension. The histologic demonstration of lymph node involvement and the development of pseudobubo in males stress the role of lymphatic dissemination from the superficial genital lesion (Table 22.1). In females, the regional lymph nodes enlarge somewhat and are occasionally tender, but they do not suppurate unless gross secondary infection of the initial lesion is present.

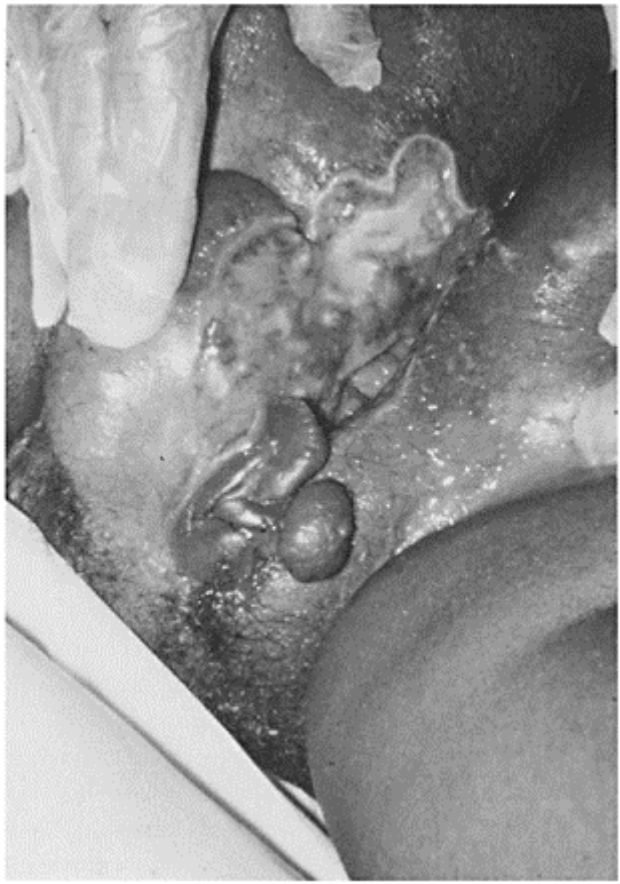

Figure 22.1 Vulval donovanosis of relatively recent origin. Some of the lesions are separate, other confluent. The margin of the lesion is raised and scrolled, and the base is granular and covered imperfectly by a thin gray slough

Biopsy of the initial lesion reveals, in addition to the secondary epithelial change, a granulomatous proliferative response and a secondary connective tissue attempt at repair. The histopathologic feature of the ulcer of donovanosis is that of a dense granulomatous tissue reaction consisting mainly of small lymphocytes, with a scattering of the typically large mononuclear cells which may contain the pathognomonic Donovan bodies. Small collections of polymorphonuclear neutrophils (microabscesses) secondary to superimposed bacterial infection are typical. In the absence of secondary infection,

neutrophils are conspicuously absent. Within the granulation tissue, capillaries tend to be prominent

Table 22.1 Differential diagnosis of inguinal adenopathy associated with a presumed venereal disease

Disease	*Genital lesion*	*Nodal involvement*	*Cutaneous lesions*
Granuloma inguinale	Extensive in males, less evident in females	Involvement of lymph nodes; draining cutaneous sinuses late in the course of the disease, nodes become tender	Primary skin infection with superficial ulceration
Lymphogranuloma venereum	Occurs, but is extremely transient in nature	Bilateral node involvement is determined by site of primary lesion	Multiple sinus tracts draining a thick, creamy exudate
Chancroid	Usually present	Primarily unilateral with limited involvement of lymph nodes	Acute, with craterlike slough
Genital tuberculosis	None	With extensive involvement of female genital tract, bilateral inguinal adenopathy	Pleomorphic, often with sinus tract draining scanty thick exudate
Syphilis	Usually present	Bilateral; firm, rubbery nodes	Protean in its clinical manifestations

owing to reactive hyperplasia of their endothelial cells. Even in the absence of Donovan bodies, the histopathology of infection due to *C. granulomatis* is sufficiently characteristic to warrant a presumptive diagnosis.

The more advanced lesions represent a composite of the two processes of exuberant granulomatous proliferation and fibroblastic repair. With partial resolution of infection, isolated foci of plasma cells and lymphocytes appear, as well as occasional macrophages within the interstices of connective tissue. With arrest of the disease process, the granulation tissue is replaced by newly grown connective tissue.

One of the less commonly seen features of the disease is a gross local swelling of the affected area. It may develop before treatment or during the phase when the ulcers are healing. These hard, knobby swellings are due to obliteration of predominantly efferent lymphatics. Biopsy of such a lesion reveals grossly dilated lymphatics.

With secondary infection of the initial ulcers, the gross appearance of the lesions changes, owing to extension of the area of ulceration deep into the underlying dermis with excavation and undermining of the margins. With appropriate therapy, the fibroblastic component predominates, leaving scar formation as the end-stage lesion of genital involvement. In 6% of the cases, extragenital lesions are observed. Metastatic hematogenous infection as well as involvement of the oral cavity has been described. The infection, particularly after delivery or abortion, infrequently extends from the cervix and may involve the uterus, fallopian tubes, and ovaries.

With extensive disease and secondary infection, systemic signs such as fever, anemia, weight loss, malaise, and leukocytosis may occur. Although the diagnosis may be inferred because of the clinical presentation and the exclusion of other disease processes, a definitive diagnosis is still contingent upon the demonstration of Donovan bodies.

DONOVANOSIS AND CARCINOMA

Infection with *C. granulomatis* is thought to be responsible for the high incidence of carcinoma of the vulva in very young patients in Jamaica. Occasionally, concomitant active donovanosis and carcinoma have been identified in the same patient. Carcinoma of the vulva occurring only a year or two after apparent cure of granuloma inguinale is one of the urgent reasons for thorough treatment and careful follow-up.

DIAGNOSIS

Many clinicians examining their first case of donovanosis think it is carcinoma, regardless of whether the lesion is of the vulva or the cervix. Adequate biopsies must be taken and carefully studied. Pathologists can also be misled. The hyperplasia and dysplasia of squamous epithelium at the edge of an ulcer can easily be mistaken for low-grade squamous cell carcinoma. Occasionally, however, the diagnosis is carcinoma.

The clinical diagnosis is suggested by the clinical appearance of the lesion or lesions. Confirmation can be obtained on the basis of histologic examination of punch biopsy material taken from the edge of active lesions, on scrapings taken from the edge of lesions, or on a crush preparation made from granulation tissue obtained with a thin scalpel. In all cases, active lesions should be cleansed with physiological saline prior to sampling. Smear preparations should be stained with either Giemsa or Wright's stain. Fixed embedded tissue specimens require the long Giemsa or silver stains. An indirect immunofluorescence test is available. This test is both sensitive and specific. Its utilization is limited by the paucity of of positive control material.

A definitive diagnosis of granuloma inguinale is almost invariably based on the identification of classic Donovan bodies in biopsy material. Donovan bodies appear as clusters of blue or black staining with an organism's 'safety pin' appearance (from bipolar chromatin) in the cytoplasm of large mononuclear cells. Biopsies should be taken radially through the edge of the ulcer and include some of its base. The affinity of the intracysts of *C. granulomatis* for silver salts facilitates the recognition of the Donovan bodies. Because Donovan bodies are very hard to find, they may be more readily demonstrated in tissue spreads stained with Giemsa's stain than in histologic sections stained with either hematoxylin and eosin or silver stains. In either case, success in their identification depends on the sharp eyes and persistence of the pathologist, who often has to search many slides in order to establish the diagnosis of donovanosis.

THERAPY

Calymmabacterium granulomatis is susceptible to a wide number of antibiotic preparations that interfere with protein synthesis. Doxycycline 100 mg orally twice a day or trimethoprim-sulfamethoxazole (two 800 mg/ 160 mg tablets every 12 hours) is the recommended initial therapy. Alternative regimen includes ciprofloxacin 750 mg po 2 times a day, erythromycin 500 mg orally 4 times a day for 21 days or azithromycin 1 g orally per week for 3 weeks. For any of these regimens, addition of an aminoglycoside (such as gentamicin 1 mg/kg IV every 8 hours) should be considered if lesions do not respond within the first few days of therapy. Doxycycline, trimethoprim-sulfamethoxazole, and ciprofloxacin are contraindicated in pregnancy

Both ampicillin and erythromycin have been found to be somewhat erratic in efficiency, the combination of ampicillin and erythromycin or azithromycin has been found to be satisfactory in the treatment of pregnant patients.

When possible, strong consideration should be given to the addition of a parenteral aminoglycoside if improvement is not evident within the first 3–4 days of therapy. Treatment should be continued until the lesions have healed completely, which usually takes three weeks. Prolonged duration of therapy is often required to permit granulation and re-epithelialzation of the ulcers. Longstanding lesions may be so mutilating that adjunctive surgical care may be necessary. The elimination of secondary infection by topical cleansing and antimicrobial therapy accelerates healing.

Relapses may occur within 6–18 months later despite effective initial therapy; some cases require prolonged courses of antibiotic therapy It is wise to treat infection vigorously and to insist on compulsive follow-up even after apparent cure.

The local areas of ‘elephantiasis’ remaining after effective treatment of active infection are often uncomfortable and cause cosmetic embarrassment. Once infection is cured, local excision of such focal swelling can be carried out.

MANAGEMENT OF SEX PARTNERS

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient’s symptoms should be examined and treated if clinical signs and symptoms are present. The value of empiric therapy in the absence of lesions has not been established.

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23
Haemophilus ducreyi

Chancroid is a superficial infection of the external genital tract caused by *Hemophilus ducreyi*. The bacteria are small Gram-negative rods measuring 0.5 μm by 1.5 to 2.0 μm, and are often seen in short chains or parallel arrays ('school-of-fish' or 'fingerprint' patterns). They may be cultivated with considerable difficulty, are nonmotile, and are not acid-fast. Bipolar staining is often demonstrable.

H. ducreyi has a worldwide distribution but is found more frequently in tropical and subtropical countries. Within the United States, there is geographic variation in disease prevalence or recognition.

CHANCROID

Chancroid has had a cyclic history in the United States. Reported cases of chancroid peaked in 1947 and then declined until 1978, when the numbers of reported cases began to rise. This increase continued through 1987 and only recently have the number of reported cases begun to decline. Considered a relatively uncommon sexually transmitted disease (STD), chancroid has become a matter for greater concern, as studies have indicated that genital ulcer is a risk factor in the transmission of HIV. The infection is disseminated venereally. Genital lesions appear three to 14 days after sexual contact and may be single or multiple. The initial lesion is usually one or more small erythematous macules which rapidly become vesicular pustules. The lesion ruptures, leaving behind a small circumscribed ulcer with an erythematous base (Table 23.1). The ulcer is painful and tender to palpation and is characterized by a nonindurated base, painful overhanging edges, and ragged margins. The lesion frequently has an erythematous halo. The base of the ulcer is covered with a dirty-looking, necrotic, grayish exudate. Lymphadenitis occurs in approximately 30% of the cases. The lymphadenopathy is regional and is often unilateral (generally on the same

Table 23.1 Clinical characteristics of chancroid ulcer

Number	usually multiple but may occur as an isolated lesion
Shape	irregular
Depth	deep
Purulence	present
Tenderness	present

Induration	none

side as the lesion). Without adequate therapy there may be extension of the process from the lymph nodes to the overlying skin, resulting in draining sinuses.

Superinfection of the ulcer or ulcers, especially by fusospirochetes, may lead to extensive destruction of the external genitalia (phagedenic chancroid).

DIAGNOSIS

Diagnosis is inferred by the demonstration of small Gram-negative rods with the so-called 'school-of-fish' appearance (Figure 23.1), occurring in strands on smears stained with Gram or Wright stain, and an ulcer characterized by non-induration of the base and painful, ragged, overhanging margins. Specific fluorescent antibody staining of bacteria in smears from suspected lesions provides a means for substantiation of the diagnosis; unfortunately, the availability of this diagnostic procedure is limited. Biopsy of the lesion is useful since it eliminates granuloma inguinale, syphilitic chancre, and herpetic ulcer from diagnostic consideration.

A definitive diagnosis is established with isolation of the organism. Gonococcal agar supplemented with bovine hemoglobin and fetal calf serum or Mueller-Hinton agar supplemented with chocolatized horse blood are required to maximize recovery on primary isolation.

Haemophilus ducreyi grows best at 35ºC in an atmosphere of 5% CO_2 in a moist environment. Single

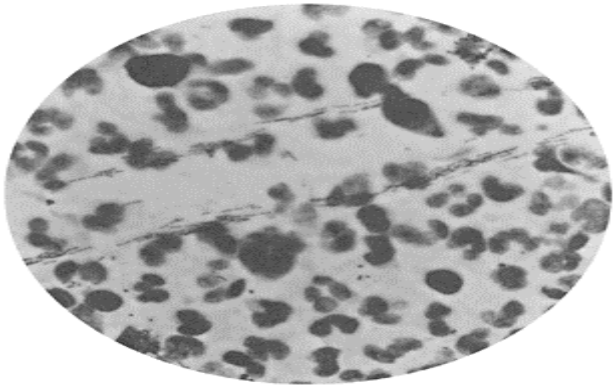

Figure 23.1 Chancroid. Gram-stained smear revealing the classic 'school-of-fish' pattern. (Parker RT. In Holly R. *Gynecology-Obstetrics Guide*. Chicago: Commerce Clearing House, 1964)

colonies are not visible until after 48–96 hours of incubation. Colonies are typically raised, opaque, compact, granular, tan or yellowish and are difficult to pick up with a loop, as colonies characteristically slide over the agar surface intact. It is the sole human *Haemophilus* species with a requirement only for X factor as determined by the porphyrin test.

Haemophilus ducreyi, being a fastidious organism that is not easily isolated and having few biochemically distinguishing features that can be used to identify it, causes concern about the sensitivity of culture identification. Many reports have suggested that the sensitivity of culture, using clinical diagnosis as the gold standard, is between 35% and 80% and these estimates appear to depend strongly on the laboratory setting; laboratories that deal with populations with a high prevalence of chancroid tend to be better able to both culture *H. ducreyi* and to diagnosis chancroid. Even with specialized culture media the sensitivity of culture identification is less than 80%.

Recently there has been increased demand for nonculture methods for the detection and identification of *H. ducreyi* and for the diagnosis of chancroid. Some progress has been made in the development of molecular diagnostic methods. These include the development of DNA probes for the direct detection of *H. ducreyi*, the development of monoclonal antibodies for detecting *H. ducreyi* in smears, and the development of serologic assays for detecting antibodies reactive with *H. ducreyi* antigens in infected individuals. In their present form, each of these methods lacks either the specificity or the sensitivity desirable in a non-culture approach for detection and identification of *H. ducreyi*.

The recent development of the polymerase chain reaction (PCR), which uses specific primers to amplify the intervening DNA sequences, may offer a sensitive and specific alternative approach for the diagnosis of chancroid.

PCR should be a useful method for the detection of *H. ducreyi* in genital lesions, particularly those in female patients where normal flora may complicate culture, and in bubo aspirates which yield positive cultures less readily than ulcers. PCR should be especially valuable for epidemiologic studies where poor culture sensitivity is a major problem, especially studies conducted with high-risk patients who are likely to have ulcers that contain multiple etiologic agents where culture sensitivity may be poorer.

Because of the possibility of concomitant syphilitic infection, darkfield analysis of all lesions should be performed. Serologic tests for syphilis should be obtained during therapy. If the antimicrobial agent utilized will not eradicate incubating syphilis, the serological test should be repeated 6–8 weeks after its termination.

A probable diagnosis for both clinical and surveillance purposes may be made if the person has one or more painful genital ulcers; and (a) no evidence of *Treponema pallidum* infection by darkfield examination of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; (b) the appearance of the genital ulcers and regional lymphadenopathy, if present, are typical for chancroid; and (c) a test for herpes simplex virus is negative. The combination of a painful ulcer with tender inguinal adenopathy (which occurs among one-third of patients) is suggestive of chancroid, and when accompanied by suppurative inguinal adenopathy is almost pathognomonic.

Table 23.2 Centers for Disease Control (CDC) 2002 recommended regimens

Azithromycin 1 g orally in a single dose
Ceftriaxone 250 mg IM in a single dose
Ciprofloxacin 500 mg orally bid for 3 days
Erythromycin base 500 mg orally tid for 7 days

HIV and chancroid

Women with HIV infection do not respond as well to treatment as do HIV-negative women. Patients should be tested for HIV infection at the time chancroid is diagnosed and retested 3 months later if the initial test results were negative.

THERAPY

The emergence of *H. ducreyi* that is resistant to multiple antibiotics has limited the effectiveness of many antimicrobials for therapy of chancroid. Trimethoprim-sulfamethoxazole (160/800 mg twice a day for seven days) had been a drug of choice. Resistance to sulfonamides is mediated by a non-conjugative 4.9 mega dalton plasmid. Because of an increasing number of treatment failures, tetracycline is no longer used for the treatment of chancroid. Worldwide, occasional isolates with intermediate resistance to ciprofloxacin or erythromycin have been reported.

The Centers for Disease Control's (CDC) recommendations for antibiotic therapy have somewhat changed from 1993 (Table 23.2). These now include: azithromycin (1 g once), erythromycin (500 mg tid for 7 days), ceftriaxone (250 mg IM once) or ciprofloxacin 500 mg bid for 3 days. Bolus ciprofloxacin (750–1000 mg) has been used with some success.

While highly effective in the treatment of chancroid, erythromycin can cause significant gastrointestinal discomfort, leading to suboptimal compliance.

Azithromycin and ceftriaxone offer the advantage of single dose therapy. Ciprofloxacin is contraindicated in pregnant and lactating women.

Ulcers in HIV-positive women do not appear to heal as readily as would be anticipated. Such patients may benefit from more intensive therapy. Irrespective of culture data, women with persisting ulcer following therapy should be considered still infected.

With effective therapy, a clinical response, first subjective and then objective, should be apparent within several days of instituting therapy. A subjective response (diminished tenderness and pain) occurs within 48 hours of institution of antimicrobials. An objective response generally occurs within 72 hours and almost always within seven days. Healing takes 10 to 11 days after institution of therapy. Large ulcers may require relatively longer time periods to heal. Patients should be seen seven days after beginning therapy, when objective signs of ulcer healing will be present in virtually all successfully treated

patients, and adenopathy should be less painful and usually smaller. Some nodes may progress to fluctuation despite adequate therapy and require needle aspiration through normal skin to prevent spontaneous drainage. Ernst *et al.* have advocated incision and drainage, with subsequent irrigation and packing of the bubo cavity. The use of a more extensive surgical procedure appears potentially applicable to large, confluent fluctuant nodes. Incisional drainage may be preferred as it will reduce need for subsequent drainage procedures.

While ulcers in successfully treated patients respond to therapy quickly, adenopathy may not, and progression to fluctuation is not necessarily a sign of treatment failure.

If by day seven a clinical response has occurred and therapy has been taken as directed, therapy need not be continued. If a clinical response is not apparent, the clinician should reconsider the clinical diagnosis of chancroid or, if it has been confirmed by a culture, consider a mixed infection, e.g. herpes and chancroid, HIV and chancroid, etc.

Sexual contacts of patients with chancroid should be examined and treated with an effective antimicrobial regimen, whether lesions are present or not, if they have had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms. Asymptomatic carriage of *H. ducreyi* appears to be uncommon, but colonization of the vagina, penis, and mouth in the absence of lesions has been described.

Initial treatment guidelines recommended that therapy be continued for at least ten days and until clinical resolution of ulcer(s) and adenopathy. Subsequent studies have shown high efficacy of one- to seven-day courses of therapy and indicate that antimicrobial courses of ten days offer no therapeutic advantage over shorter courses, even though ulcers have not completely healed and adenopathy is persistent.

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24
Haemophilus influenzae

The bacterium *Haemophilus influenzae* was initially described by Pfeiffer who presumed it to be the causative agent for the 1889–1891 influenza pandemic. The organism is a Gram-negative aerobic bacillus which requires both X factor (hemin) and V factor (nicotinamide adenine dinucleotide). X factor is released into the medium by red blood cells. While V factor is also present in red blood cells, it is not released into the medium unless the cells are lysed. Consequently, *H. influenzae* will not grow on blood agar except as satellite colonies around other colonies which produce hemolysis.

Haemophilus influenzae is classifiable by virtue of its capsular polysaccharides into six typeable serotypes (a, b, c, d, e, and f) and into non-typeable strains. The type b and non-typeable strains are the principal causes of disease. Of the typeable strains, type b is the most virulent.

Based upon three biochemical reactions, the organism can be classified into six biotypes. Most *H. influenzae* type b are biotypes I and II whereas most non-typeable strains are II through VI (Table 24.1). Nearly all genital isolates of *H. influenzae* from puerperal women with endometritis and hematogenous isolates from infected neonates are biotype IV (Table 24.2). In contrast, bio-type I accounts for 80% of septicemic isolates in children. Respiratory isolates from well children and children whose illness was not caused by *H. influenzae* were rarely serotypeable (1%) or were biotype I (8%). The predominance of biotype I in invasive disease argues that these strains possess unique virulence determinants.

Haemophilus influenzae is a rare constituent of the vaginal flora. Khuri-Bulos and McIntosh failed to recover *H. influenzae* in 325 cervical cultures obtained from obstetric patients. Other studies have shown rates of isolation of less than 0.02%.

As a monoetiological pathogen, *H. influenzae* produces four disease entities which are specific for the female genital tract and/or products of conception:

(1) acute bacterial vulvovaginitis;
(2) hematogenous and ascending chorioamnionitis;
(3) endometritis; and
(4) perinatal septicemia.

In addition, the non-typeable strains can function as part of the anaerobic progression.

CLINICAL DISEASE

Acute bacterial vulvovaginitis

Haemophilus influenzae can be a cause of vulvovaginitis and should be treated as an exogenous pathogen in this clinical setting. It produces a purulent vaginitis. The onset of the disease is sudden. Vaginal erythema and pressure tenderness are two characteristics. The recovery of this bacterial species from the female genital tract should have the same significance to a clinician as that of the group A beta-hemolytic streptococci.

Chorioamnionitis/perinatal septicemia

In contrast to the group B streptococci with their high prevalence of genital tract colonization but low attack rate, *H. influenzae* appears to have a low prevalence, but a high attack rate in terms of maternal and neonatal infection. When present, the organism has the potential to cause both local and systemic disease. If rupture of the fetal membranes ensues, chorioamnionitis frequently ensues; however, the majority of affected infants are born to mothers in whom rupture of the fetal membranes did not constitute a significant antepartum obstetric

Table 24.1 Relationship of serotypes and biotypes of *Haemophilus influenzae*

Serotype	***Biotype***
Type b strains	Biotype I and Biotype II (I and II)
Non-typeable strains	Biotypes II through VI

Table 24.2 Relationship of serotypes to specific disease entities due to *Haemophilus influenzae*

Type B strain	***Non-typeable strains***
Meningitis*	Acute sinusitis
Otitis media	Chronic bronchitis
Cellulitis*	Acute tracheobronchitis
Epiglottitis*	Pneumonia
Septic arthritis*	Chorioamnionitis (ascending)
Chorioamnionitis	
Endometritis (hematogenous)	

Perinatal septicemia	
Vulvovaginitis	

*Specific for type b strains

complication, implying hematogenous dissemination. In the majority of cases of neonatal septicemia, maternal colonization or infection with *H. influenzae* can be demonstrated. In one series of 10 cases of neonatal septicemia due to *H. influenzae*, type b was responsible for disease in four of the neonates. The strains were not typeable in four and not typed in the remaining two cases. Maternal infectious febrile morbidity occurred within 24 hours of fetal membrane dissolution in six of the 10 cases. Prolonged rupture of the fetal membranes in combination with endocervical colonization has a higher correlation with postpartum maternal infectious morbidity than with neonatal disease. Rusin *et al.* analyzed the records of all mothers and neonates infected with *H. influenzae* over a 10-year period. Of the 18 infected mothers, 13 had chorioamnionitis, endometritis, or both. Of the 23 infected neonates, 15 presented with early sepsis and/or pneumonia and nine had conjunctivitis. During the period of the study, only group B streptococci and *Escherichia coli* were more common as causes of early neonatal bacteremia. Under the conditions of this retrospective study, maternal infection predicted neonatal infection.

Endometritis

In the female genital tract, non-encapsulated *H. influenzae* organisms appear to function as pathogens when there is pre-existing disease. *H. influenzae* has been recovered from cases of chronic endometritis associated with the Lippes loop intrauterine contraceptive device (IUD) and from tubo-ovarian abscesses.

Salpingitis

Salpingitis due to *H. influenzae* has traditionally been associated with IUD usage. Recently Carmeci and Gregg have reported a case of *H. influenzae* acute salpingitis in a patient who had no predisposing conditions.

DIAGNOSIS

As previously indicated, *H. influenzae* will not grow on blood agar, except as tiny colonies around other bacterial colonies which produce hemolysis of the red blood cells. Recovery of the bacteria can be readily achieved on chocolate agar. Dependence on X and V factors is demonstrable with horse blood and brain heart infusion plates. Definitive confirmation is achieved by the Quellung reaction using type-specific antiserum.

When present, capsular antigens can be detected by latex agglutination or enzyme-linked immunosorbent assay (ELISA).

Haemophilus influenzae may be responsible for false-negative blood cultures if routine ‘blind’ subcultures of grossly negative cultures are not performed within 12 to 16

hours after blood collection. Subcultures should be inoculated onto quadrants of chocolate agar plates which are incubated in 10% CO_2 for 48 hours.

THERAPY

Ampicillin was once considered the drug of choice; however, therapy of disease is complicated by the

Table 24.3 Therapeutic considerations for *Haemophilus influenzae*

Antibiotic	***Limiting factors***
Ampicillin	25% of *Haemophilus influenzae* type b show
Third-generation cephalosporins, i.e., ceftizoxime and cefotamine	resistance to penicillin and semi-synthetic analogues

progressive development of antibiotic resistance due to the production of (3 lactamases (Table 24.3). Approximately 25% of *H. influenzae* type b strains are resistant to penicillin and its semi-synthetic analogues. Current therapy focuses on selected 'third generation' cephalosporins (cefuroxime 0.75–1.5 g every eight hours, ceftriaxone 1.0–2.0 g every 24 hours, or cefotaxime 1.5–2.0 g every eight hours).

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25
Listeria monocytogenes

Listeria monocytogenes is a member of the family Corynebacteriaceae, order Eubacteriales. It is a small, slightly curved Gram-positive and catalase-positive bacillus with rounded ends. The organism can exist in both a rough form and the predominantly pathogenic smooth form which is characterized by a peritrichous arrangement of flagella. These flagella are responsible for the tumbling motility seen when the organism is grown in cultures at room temperature. Old cultures, particularly if incubated at 37ºC, show imperceptible movement. The organism ferments several carbohydrate substances; however, the fermentative reactions are neither sufficiently characteristic nor consistent enough to be of much diagnostic significance. *L. monocytogenes* produces soluble hemolysins which may cause a very narrow band of beta-hemolysis on blood agar plates.

There are 11 serotypes of *L. monocytogenes*, 1a, 1b, 2, 3a, 3b, 4a, 4b, 4ab, 4c, 4d, and 4e, based on analysis of somatic and flagellar antigens. It is generally stated that type 1 serotypes tend to be predominantly isolated from rodents, whereas type 4 serotypes tend to be isolated from herbivores; however, there is no absolute species specificity. Dissemination is believed to be primarily foodborne.

The majority of human infections that have been serotyped belong to the group 3 serotypes. As might be anticipated from its characteristic pathology, abscess formation, the organism is a facultative anaerobe. Certain facets of the pathogenesis of the morphologic lesion are thought to be the consequence of host response to a toxin, even though no toxin has yet been identified.

Much speculation exists as to whether or not there may be a filterable L form of *L. monocytogenes*. The presence of an L form has been postulated as one of the reasons for the difficulties in isolating the bacterium from infected tissue as opposed to biologic fluids such as cerebrospinal fluid (CSF), urine, and blood.

CLINICAL DISEASE

Depending upon the patient population infected, *L. monocytogenes* produces primarily two diverging patterns of disease. In immunologically compromised or age-vulnerable populations, infection results in invasive disease. Among patients with advanced human immunodeficiency syndrome, listeriosis is approximately 100 times more frequent than in the general population. The clinical presentation tends to be sepsis, meningitis, meningoencephalitis, cerebritis or brain abscess. Disease selection reflects the importance of the T-helper cell-mononuclear phagocyte arm of the immune defense system in organismal containment. Fetuses and neonates constitute an age-vulnerable population.

In non-immuno- or disease-compromised populations, clinical presentation is primarily that of a gastrointestinal illness or infectious mononucleosis-like syndrome.

Maternal listeriosis

Infection has a predilection for pregnant women. *Listeria monocytogenes* produces a spectrum of disease. Because of the forme fruste of disease and the ability to mimic other infections, the clinical diagnosis of *L. monocytogenes* is often difficult.

When clinically overt, *L. monocytogenes* may present as one of three syndromes:

(1) infectious mononucleosis-like syndrome;
(2) influenza-like syndrome;
(3) typhoidal-like syndrome; and
(4) febrile gastroenteritis.

Approximately 20% of infants with neonatal listeriosis are born to asymptomatic gravida. The infectious mononucleosis-like syndrome is characterized by malaise, chills, fever, pharyngitis, lymphadenopathy, splenomegaly and monocytosis. The influenza-like pattern is characterized by fever, headaches, and upper respiratory symptoms. Some women experience a very transient macular salmon-colored rash. Careful questioning of these patients reveals the majority to have one or more documented episodes of rigors. The typhoid-like syndrome is characterized by high spiking temperatures which are often associated with back pain or flank pain. In many instances, the diagnosis of pyelonephritis is made even though there is no subsequent substantiation by urinalysis or urine cultures. *Listeria monocytogenes* can cause a febrile gastroenteritis characterized by fever, musculoskeletal symptoms, nausea, vomiting and diarrhea. Foods incriminated as the vehicle source have included soft cheese, shrimps, foods sold from delicatessen counters, rice salad, pork tongue in jelly and undercooked chicken.

The dose inoculum of bacteria influences the timing and probability of disease. While most of the gastrointestinal symptomology develops within a few days following ingestion of the contaminated food, Riedo *et al.* reported incubation periods in two pregnant women of 19 and 23 days.

Individuals infected with human immunodeficiency virus (HIV) are at greater risk of infection with *Listeria monocytogenes* than the general population. Ewert *et al.* quantified the risk of listeriosis in persons with acquired immune deficiency syndrome (AIDS) and HIV infection in Los Angeles County. The incidence of listeriosis was 95.8 and 8.8 cases per 100000 person-years among persons with AIDS and all HIV-infected persons, respectively, but only 1.0 case per 100000 person-years in the total population. When disease occurs in an immunocompromised gravida, greater morbidity is likely to ensue.

In the majority of instances, the mother is not critically ill, the symptoms are of relatively short duration, and with or without therapy the fever, pain, and associated symptoms will subside. The impact on the fetus is usually delayed for several days or weeks. Fetal death *in utero* may occur. This is usually heralded by diminution and finally total cessation of fetal movements. Alternatively, parturition may ensue with delivery of a stillborn or severely ill infant. Occasionally, fever occurs or recurs with the onset of labor, and the amniotic fluid and fetal surfaces of the placenta are often suggestive of chorioamnionitis. In rare instances, careful inspection of the placenta reveals small miliary areas of necrosis. In many instances, the amniotic fluid will have a murky discolored appearance. In those instances in which the gravida is febrile and symptomatic prior to parturition, she often becomes asymptomatic postpartum, and her clinical course tends to be uneventful even in the absence of therapy. In rare instances, maternal

infection may result in meningitis which cannot be distinguished from meningitis due to other bacteria. There is no characteristic body of laboratory data or clinical profile. In most instances, the organism is readily identified in the CSF. In retrospect, one is often able to elicit a history of a prodrome of either gastrointestinal upset with diarrhea or respiratory infection and then ensuing headaches, myalgia, fever, chills, nausea, vomiting, and stiff neck. In the absence of therapy, mortality exceeds 70%. The correct diagnosis is usually made as a consequence of recovery of the organisms from the blood or CSF.

Patients without significant symptomatology will have the diagnosis of listeriosis made retrospectively, only after the delivery of an infected or stillborn infant. A significant number of cases of perinatal septicemia occur in the progenies born to asymptomatic mothers who experience no obvious illness during pregnancy. Maternal septicemia may occur both with disease and infection. What does maternal septicemia mean in terms of potential fetal involvement? Data in the literature indicate a near one-to-one correlation between symptomatic maternal listeriosis and subsequent involvement of the products of conception. *L. monocytogenes* can be isolated from amniotic fluid in cases of congenital infection and from the neonates or products of conception in cases after documented maternal septicemia. In the absence of therapy, when *L. monocytogenes* is isolated from the intravascular compartment of gravida, the fetus almost invariably becomes infected.

Genital listeriosis

There has been much speculation as to whether or not *L. monocytogenes* may result in prolonged colonization of the female genital tract. Circumstantial evidence indicates that *L. monocytogenes* may be spread by venereal modes of transmission. The organism has been isolated from urethral exudates of individuals with gonorrhea who shared a common sexual partner, as well as from the semen of consorts of women who had genital listeriosis. None of the men with genital listeriosis exhibited urethral symptoms; however, analysis of their semen prior to therapy showed reductions in sperm count and motility viability as well as incomplete mucolysis of seminal fluid in the ejaculate. With therapy, the impaired sperm indices returned to normal. In European countries, there is a high incidence of isolation of the organism from women with histories of repeated abortions. In one study, *L. monocytogenes* was recovered from 25 of 34 women with a history of repeated abortion. Diagnosis was contingent on the isolation of the organism from at least three cultures taken at 1–5 day intervals. Three of the patients were pregnant and in the second trimester. All three aborted shortly thereafter. In one instance *L. monocytogenes* was isolated from the amniotic fluid. The remaining eight gravidas were in their first trimester. They received antibiotic therapy, and no ensuing fetal deaths were observed.

Chronic infection of the female genital tract is thought to be manifested by continuous excretion of the microorganisms from the uterine cervix over long periods, which may result in abortion or stillbirth in a supervening pregnancy. The observations cited are only suggestive, and much more of the natural history of infection must evolve before these fragmentary pieces of knowledge can be put into proper perspective.

Congenital and neonatal infection (granulomatosis infantiseptica)

There have been recent attempts to divide neonatal listeriosis into early-onset and late-onset disease. Early-onset disease becomes clinically apparent within the first five days of life; late-onset, after more than five days. Unfortunately, this classification, borrowed from group B streptococcal infections, amalgamates congenital infection with early neonatally acquired infection despite their markedly different pathogenesis.

In most instances, congenital listeriosis is the consequence of seeding of the fetal compartment by a low-grade maternal septicemia. Almost invariably, microscopic listerial placentitis can be demonstrated, with involvement of the maternal placental component and subsequent extension of the disease process to the fetal compartment. The majority of mothers exhibit clinical illness characterized by pyrexia. Not infrequently, the amniotic fluid is discolored in appearance resembling 'murky dish water'. When in gestation maternal disease occurs partially dictates the neonatal consequences in the absence of therapy. First trimester maternal infection results in abortion. Fetal death *in utero* is a common occurrence when disease occurs in the second trimester. Third trimester infection or disease produces premature termination of pregnancy. Of those infants born alive, many die within minutes after parturition. The bacteria recovered from the female genital tract are of the same serotype as those which infect the infant. No particular serotype predominates. Congenital listeriosis may account for up to 20% of perinatal septicemia. Up to 60% of cases of congenital listeriosis present as preterm labor.

Listeria monocytogenes is endemic in both wild and domestic animals. A small but significant number of humans may function as fetal carriers of the organism for limited periods of time. It is probable that birds and mammals constitute the major reservoir of listeriosis and, in certain instances, are directly responsible for human infection. Direct contamination of fruits and vegetables as well as unpasteurized milk have been the source of mini-epidemics. Schwartz *et al.* analyzed over 50 cases of perinatal listeriosis. The only statistically significant demographic difference was a history of having eaten uncooked hot dogs or undercooked chicken.

According to Farber and Losos, *L. monocytogenes* can be recovered from a variety of dairy products, leafy vegetables, fish and meat products. It can be isolated from refrigerated foods and is more heat-resistant than most vegetative bacteria. Epizootic listeriosis occurs in laboratory animals and cattle. Disease in man is a sporadic event; however, when it does occur, not infrequently a second or third case will be identified at the same institution within several months of each other. Though occurring in unrelated patients, these mini-clusters of cases are usually due to a common serotype. Other than some rare cases of apparent neonatal cross-infection in nurseries, person-to-person transmission, with the exception of venereal, has not been recognized.

Listeria monocytogenes is rapidly becoming one of the more important bacterial infections which involve both the gravida and her fetus. The incidence of perinatal infection with *L. monocytogenes* is higher than the 1 in 30000 births reported in England by the Communicable Disease Surveillance Centre. In the past decade, the incidence of disease has increased such that, in a number of institutions in the United States, *L. monocytogenes* is the third most common bacterial cause of perinatal septicemia (septicemia in the first 24 hours of life). The unique importance of *L. monocytogenes* is that, if left untreated, it results in a high perinatal mortality. Disease in the mother usually

spontaneously regresses. Sixty percent of neonates die due to the infection. Another 30% have permanent sequelae. However, if identified and properly treated, the disease can be totally eradicated *in utero*.

Live-born infants exhibit evidence of central nervous system involvement, manifested by fever, abnormal patterns of respiration, and the subsequent onset of vasomotor collapse. Occasionally, a rash associated with cutaneous bacterial involvement is observed. The majority of infants with congenital infection will have roentgenographic abnormalities. These range from interstitial pneumonitis to nodular infiltrates. While group B streptococci can emulate these findings, it is relatively rare for *L. monocytogenes* to mimic the roentgenographic picture of hyaline membrane disease. The neonates surviving parturition are often critically ill and not infrequently succumb during the first or second week of life from cardiovascular collapse and pulmonic involvement. Therapy requires vigorous ventilatory support and aggressive antibiotic therapy with ampicillin. If evidence of a left-to-right shunt or pulmonary hypertension is documented and the infant cannot be adequately ventilated, attempts should be undertaken to combat the associated pulmonary vasospasm which seems to aggravate the hypoxemia.

While congenital infection secondary to hematogenous dissemination is the most characteristic mechanism for granulomatosis infantiseptica, it does not represent the sole mechanism by which the fetus or neonate may become infected. Transperineal spread of the ingested *L. monocytogenes* can result in vaginal-cervical colonization and a possibility of ascending infection.

The probability of sexual transmission has been inferred by the identification of the organism in semen of sexual consorts of women with recurrent abortions. Once effective labor has been established and/or dissolution of the fetal membranes has occurred, potential for ascending infection occurs. The clinical picture here is that of chorioamnionitis. An alternative presentation for these patients is relatively asymptomatic disease in the gravida with the major symptoms being that of premature labor. Transabdominal amniocentesis has documented, in rare instances, that the onset of labor in the late second or early third trimester was due to *L. monocytogenes*.

Infected neonates can be the source for hospital-acquired meningitis and enterocolitis within intensive care nurseries.

Neonatally acquired listeriosis is somewhat analogous to the problems observed with group B streptococci. Two patterns of disease exist: an early-onset septicemia and a late-onset meningitis. The early-onset septicemic form is observed in progeny of mothers with obstetric complications; it has a proclivity for premature infants and is associated with a high neonatal mortality rate.

Neonatal presentation is primarily a function of the portal of infection. When the organism has been inhaled, the principal manifestations of disease are respiratory distress, apnea, cyanosis, hypothermia and bradycardia. The majority of infants have roentgenographic evidence of disease. In other instances, the conjunctiva or nasopharynx has provided the portal of infection. These patients present with a septicemic/meningitis type of onset which has been termed as late-onset as opposed to early-onset respiratory distress. These children develop hepatosplenomegaly, conjunctivitis, cutaneous manifestations of disseminated and vascular coagulopathy and sometime ascites.

The characteristic pattern of late-onset disease is that of meningitis. Disease occurs in normal neonates with no antecedent history of infectious complications. In contrast to the

meningitis due to *Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae,* disease tends to occur in the fourth week. The most frequent presenting manifestations, in addition to fever, are irritability and anorexia. Less frequent signs include respiratory distress, lethargy, cyanosis, jaundice, tense anterior fontanelle, and convulsions. Differential cell counts of white blood cells in the CSF demonstrate a polymorphonuclear neutrophilic leukocytosis. A relative or absolute monocytosis occurs in approximately 30% of the cases.

The organisms responsible for late-onset neonatal meningitis tend to be serotypes 1 and 4. The mortality figures are far more favorable than those observed with early-onset septicemic disease. Approximately 50% of the infants survive; however, late sequelae including hydrocephalus and mental retardation may occur.

At autopsy one finds widespread miliary micro- and macro-abscesses, primarily involving the liver, spleen, adrenal glands, lung, gastrointestinal tract, central nervous system, and skin. These foci of septic necrosis are manifested as grayish white, often slightly raised, pinhead lesions. The hepatic abscesses characteristically border on central veins. The organism can be readily demonstrated with appropriate bacterial stains, both lying free and phagocytized within polymorphonuclear (PMN) neutrophils. As is obvious from this description, granulomatosis infantiseptica is a misnomer. The name originated because the gross lesions resembled those seen in miliary tuberculosis.

Invasive disease is more likely to occur in HIV-postive gravida and to result in more serious adverse outcomes.

DIAGNOSIS

The diagnosis requires a high index of suspicion. The presence of Gram-positive coccibacilli in meconium gastric aspirates or CSF may make the presumptive diagnosis of neonatal listeriosis. The diagnosis can be inferred by finding widespread miliary microabscesses involving the placenta which, when Gram stained, reveal the presence of the characteristic coccobacillus, both lying free and within PMN neutrophils. When available, definitive confirmation can be achieved using a direct immunofluorescent technique. Unless the laboratory is appropriately alerted to possible isolation of *L. monocytogenes,* because of the morphological similarities between *L. monocytogenes* and other members of the genus *Corynebacterium,* positive cultures may be discarded as diphtheroid contaminants. A laboratory report of diphtheroids, especially in pure culture from certain types of infection (i.e. meningitis, neonatal septicemia or chorioamnionitis), should raise the possibility of false identification and a suspicion of underlying listeriosis. *L. monocytogenes* can be grown from blood and CSF; however, its isolation from tissue sources may be difficult. Once growth is achieved on artificial medium, the bacteria grow well on common, commercially available media. If recovery of the organism is to be attempted from tissue, it is best that the material be kept at 4ºC for one to two days before inoculation into a bacteriological media. *L. monocytogenes* can be differentiated from diphtheroids by its motility at 20–30°C. A clinician who challenges the diagnosis of the diphtheroids can ask for the intraperitoneal inoculation of the isolate into seronegative mice. If the isolate is *L. monocytogenes,* intraperitoneal inoculation of 0.1 to 0.2 ml of a 24-hour culture of diphtheroids will result in the demise of the mouse in one to three

days. Autopsy will reveal miliary abscesses involving primarily the liver, spleen and mesenteric lymph nodes. Gram stain of these nodes reveals Gram-positive rods. In the majority of instances, the diagnosis of listeriosis is derived by bacteriological identification from blood or CSF.

THERAPY

The keynote of maternal therapy is prompt institution of effective antibiotic therapy. The variation in resistance to antibiotics exhibited by different strains of *L. monocytogenes* poses a problem in empiric treatment. Patients with overt listeriosis should receive parenteral therapy. At present, the combination of ampicillin and aminoglycoside appears to afford the best therapy.

If the gravida is allergic to penicillin (immediate type of reaction or definite history of hypersensitivity), trimethroprim-sulfamethoxazole, 20 mg/kg/day of the trimethoprim component in four divided doses, or erythromycin 60 mg/kg/day intravenously in four divided doses can be utilized. Erythromycin traverses the placental barrier poorly. The recommended duration of therapy in symptomatic patients is 14 days; however, shorter courses of drug administration, 5 to 7 days, have been effective. Because of the uncertainty of the initial maternal diagnosis, combined antibiotic therapy with ampicillin and an aminoglycoside is often used effectively. What is of the utmost importance is that when infection with *L. monocytogenes* is suspected the cephalosporins should not be used. The cephalosporins are ineffective in the therapy of listeriosis.

A growing number of reports indicate that good reproductive outcome can be achieved if transplacental infection can be arrested *in utero*. Therapeutic concentrations of ampicillin can be achieved in amniotic fluid. A number of cases of maternal listeriosis septicemia have been reported in which systemic antibiotics resulted in a favorable pregnancy outcome. The growing documentability of successful treatment of potentially lethal fetal disease due to *L. monocytogenes* places a premium on excluding this disease entity when a gravida presents with rigors and/or flu-like syndrome.

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26
Neisseria gonorrhoeae

Neisseria gonorrhoeae is a Gram-negative, kidney-bean-shaped diplococcus measuring 0.6–1 μm in diameter. It is a strict aerobe which requires humidity and CO_2 for growth. Optimal growth occurs at 34º–36ºC and a pH range of 7.2–7.6. Prior therapy with penicillin or its synthetic analogues can significantly alter both the characteristic bacterial morphology and the stainability, thus on occasion obscuring diagnosis from Gram-stained smears. Inhibition of cell wall synthesis by the penicillins causes the organism to lose its characteristic kidney bean-shape as well as its ability to stain Gram-negative.

The organism is a pathogen for columnar and transitional epithelium. Infectivity appears to be in part a function of the presence of hair-like structures, pili, which may be important for the initial attachment of the gonococci to epithelial J cells. Five distinct colony forms have been identified: fresh isolates exhibit colony forms T1 and T2 characterized by the presence of pili and by virulence on experimental inoculation into the urethra of male chimpanzees. Repeated subculturing of these isolates produces the T3, T4, and T5 colony forms, which lack pili and are less virulent.

The determinants of disease are difficult to distinguish. Prior infection does not confer immunity either systemically or at the portal of infection. Although volunteers with circulating antibodies are more resistant to experimental infection than those without, humoral immunity *per se* is not the critical factor in determining the attack rate. Disease can recur in the presence of specific antibodies. The virulence of *N. gonorrhoeae* may vary. Some men do not acquire the disease and others do when exposed to the same asymptomatic female carrier.

Two factors which permit infection to become disease are:

(1) dissolution of the anatomicophysiologic barrier constituted by endocervical mucosa; and
(2) the marked alteration in pH induced by menstrual blood.

The timing of the onset of acute salpingitis due to *N. gonorrhoeae* is such that it frequently occurs at or immediately following menses. In the gravid female, the rarity with which the gonococcus establishes overt disease in the endometrium and fallopian tubes after the first eight weeks of pregnancy indicates the efficacy of the endocervical barrier to ascending infection.

FEMALE GENITAL TRACT INVOLVEMENT

Acute salpingitis

Gonococcal disease involving the female genital tract is characterized by:

(1) penetration of the glandular mucosa; and
(2) submucosal lymphatic and contiguous surface spread.

Once infection is established within the endometrial cavity, the gonococcus takes the path of least resistance. Involvement of the female genital tract is one of sequential infection due to contiguous bacterial replication and dissemination along the epithelial surfaces and to submucosal lymphatic spread. This is in marked contrast to the infectious mechanism of bacteria such as the group A streptococci which, once having penetrated the glandular epithelium, pursues a transorgan route so as to involve sequentially the endometrium, the myometrium, and then adjacent soft tissues or the peritoneal serosa.

Peritonitis secondary to *N. gonorrhoeae* is primarily the consequence of spillage of organism and inflammatory exudate from the fimbriated ends of the fallopian tube into the peritoneal cavity, and not of transmural infection. Although the capsular surface of the ovary may be superficially involved in acute gonococcal salpingitis, it is resistant to penetration of the organism. Once having attained access to the peritoneal cavity, the gonococcus may again spread along free surfaces and up the paravertebral gutters to produce a perihepatitis known as the Stajano-Curtis-Fitz-Hugh syndrome (see Gonococcal perihepatitis).

Currently, gonorrhea is the second most prevalent reportable infection in the United States. Over one and a half million new cases develop annually. Moreover, it is estimated that over sixty million new cases develop annually in the world. The relative inability to eradicate the disease is in part due to the fact that asymptomatic women with gonorrhea provide a great reservoir of infection that perpetuates the organism within the population. It is becoming apparent that significant control of the disease can only occur if routine cervical and anorectal cultures become a standard part of comprehensive female health care.

Clinical aspects

Generally, in men, the initial symptoms due to infection with the gonococcus appear 3–5 days after sexual exposure. In women, the interim between colonization and disease is so variable as to preclude a meaningful estimate. The susceptible genital areas that have been exposed are the urethra, paraurethral glands, and cervix. When the first two areas are involved, the symptoms produced may be so minimal that the patient is unaware of them. They include urinary frequency and slight burning on urination. When the endocervix is infected, vaginal leukorrhea not infrequently develops. The discharge may not be any more profuse than one which already existed; however, its appearance may be altered. It is now likely to be green or yellow-green and may be irritating to the vulvar tissues, whereas the previous discharge was not. Examination is rarely performed at this time, as the symptoms are usually not severe enough to compel the patient to seek medical advice.

The infection may extend to involve Bartholin’s glands and may advance to abscess formation. It is a mistake to think that all Bartholin abscesses are gonorrheal, since they can develop from other types of infection. Local redness, swelling, and edema as well as pain are present. As the abscess enlarges, it approaches the surface and may undergo spontaneous rupture. The pain may be sufficiently severe to require incision and drainage. Spontaneous resolution may occur, with cyst formation or the development of a

nodular swelling that remains deep at the site of the gland. The symptoms generally subside after several days or a week, even if untreated. The gonococcus, if present at the start of the disease, is often eliminated from the site of infection by obligatory anaerobic bacteria once abscess formation is well established.

Progress of disease

The organisms in the endocervix are probably prevented from progressing upward to the endometrium by cervical mucus. With the onset of menses, the bacteria may gain entrance to the uterine cavity. Menstruation not only negates the effect of cervical mucus and destroys the barrier constituted by the intact endometrium, but renders vaginal pH more alkaline, thus favoring the growth of *N. gonorrhoeae*.

Gonorrheal endometritis is transitory and heals spontaneously without leaving its mark. The organisms spread quickly and bilaterally to the endosalpinx and then, by virtue of the pus that pours from the fimbriated end of the tube, the infection involves the ovaries, the cul-de-sac, and the pelvic peritoneum, producing pelvic peritonitis.

Neisseria gonorrhoeae by virtue of its replication alters the local microbiologic environment. The lowered oxidation-reduction potential permits selected constituents of the vaginal flora to successfully compete in this biologic niche. Initially, the bacteria recruited are Class I anaerobes. By virtue of local consumption of molecular oxygen, pH changes and lowering of the oxidation-reduction potential, the microbiologic environment becomes progressively more conducive for anaerobic bacteria until a point is reached at which the aerobic bacteria, such as *N. gonorrhoeae,* undergo auto-elimination. It is currently postulated that the critical site of infection in acute salpingitis is interstitial rather than intraluminal. As in patients with pyelonephritis, the consequence of basement membrane destruction secondary to the interstitial inflammatory process is healing by fibrosis. The destructive changes which alter the normal fallopian tube structure are due not primarily to *N. gonorrhoeae,* but to anaerobic bacteria, which function at these interstitial sites.

Although the endosalpingitis is the predominant feature of the infection, infection may spread both into the muscle wall of the tube and into the broad ligament tissues. Grossly, the tube is swollen, containing purulent material within its lumen that exudes from its fimbriated end. In severe cases the tube may be covered with a shaggy fibrinous exudate. The vessels are engorged. The pelvic peritoneum and ovaries are inflamed; turbid fluid or pus may be present in the pelvis. Microscopically, this stage is characterized by hyperemia, marked edema of the tubal folds, and leukocytic infiltration.

Symptomatically, there may be fever (up to 40ºC); nausea and vomiting are not uncommon; and pain, moderate or severe, is usually present and generally located in both quadrants of the lower abdomen. Although one side may manifest greater involvement than the other, rarely will only one side be involved.

On examination, there is tenderness and variable rigidity in both lower quadrants; there may also be some distention. On pelvic examination, evidence of infection of the external genitalia and cervix may be present; motion of the cervix causes pain and there is tenderness in the lateral fornices.

Without the treatment, the symptoms and the findings described begin to subside in about 7 to 10 days and are usually gone in about 21 days. Uncomplicated gonococcal salpingitis responds to appropriate antibiotic therapy in 24 to 48 hours.

Acute salpingitis and the IUD

When a gonococcal infection occurs in a woman with a contraceptive intrauterine device (IUD), she has a three- to fourfold greater chance of developing acute salpingitis than an asymptomatic carrier without an IUD. In selected instances, the IUD may facilitate secondary infection by anaerobic organisms (in particular, *Bacteroides* and peptostreptococci).

Gonococcal septicemia

Most loci of gonococcal infection are the consequence of contiguous spread by the organism. There are two syndromes which may either occur independently or co-exist in a patient, that are the consequence of hematogenous dissemination: gonococcemia and gonococcal arthritis.

Not infrequently a patient may exhibit small, raised macular skin lesions, which preferentially involve the wrists and distal joints. The lesions may become pustules (Figure 26.1). Gonococcemia is usually associated with migratory polyarthralgia or arthritis. Fever occurs in 85% of the cases. The differential diagnosis includes meningococcemia, rickettsial infection, and subacute bacterial endocarditis. Unlike meningococcemia, gonococcemia is relatively benign in its morbidity and mortality. Since the initial clinical presentation may be indistinguishable from meningococcemia or subacute bacterial endocarditis, the patient should initially receive 20 million units of penicillin G intravenously in the first 24 hours after a minimum of three sets of blood cultures have been obtained. Once the diagnosis of *N. gonorrhoeae* septicemia has been documented, the dosage of penicillin can be substantially reduced.

Prolonged disseminated gonoccocal infection, like meningococcemia, may be due to an inherent absence of the fifth component of complement (C_5). The importance of C_5 in host susceptibility to invasive *Neisseria* infections has been inferred by epidemiological studies of females with this terminal complement component deficiency. Complement mediated bacterial lysis appears to be important in human defense against bacteremic *Neisseria* infections. Peter *et al.* reported a family in which the oldest male child had suffered severe and recurrent meningococcal meningitis over four years (at ages 14 and 18 years), and a sister had the gonococcal arthritis-cutaneous syndrome. Bacterial disease in the absence of C_5 due to *N. gonorrhoeae* usually occurs in adolescence and early childhood.

All patients with prolonged gonococcal bacteremia or gonococcemia should be analyzed for complement deficiency syndrome. Once identified, the entire family should be screened.

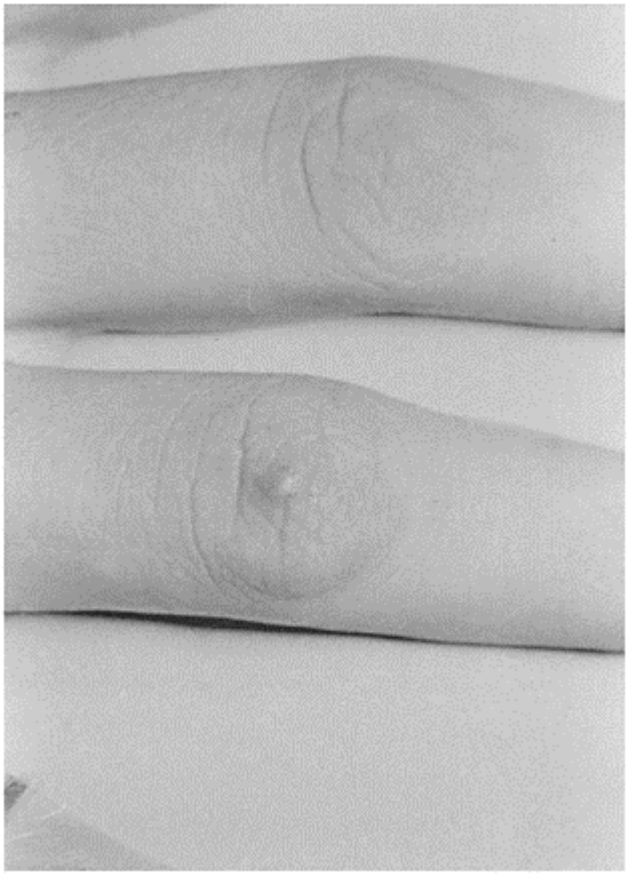

Figure 26.1 A vesiculopustular lesion on the middle finger of a young woman with disseminated gonococcal infection

While host considerations may be of prime importance in gonococcemia-like disease, the isolates from patient to patient with disseminated gonococcal infection appear to be significantly different from other gonococcal isolates. The majority of the isolates are of an auxotype different from that of most other gonococci. They are not killed by sera from other patients with uncomplicated gonorrhea, even though these sera are bactericidal to other gonococci.

Gonococcal arthritis

While acute gonococcal salpingitis in pregnancy is rare, gonococcal arthritis is not. The prompt and effective treatment of symptomatic primary gonorrhea has shifted the sex

ratio of gonococcal arthritis. The majority of the current cases are in women, and, in particular, in gravidas. The absence of genitourinary signs often obscures early diagnosis and therapy. What is termed gonococcal arthritis is in most instances a tenosynovitis and not a true arthritis. Tenosynovitis, particularly of the wrist, is common in gonococcal arthritis, whereas it is rare in other types of pyogenic arthritis.

Gonococcal arthritis tends to take one of two forms: a septic form in which the patient gives a history of chills and fever, or a non-septic form in which there is no evidence of bacteremia or skin lesions comparable to those observed in meningococcemia. In approximately 85% of cases the arthritis is polyarticular. Even in its septic mono- or oligoarthritis form, which involves large joints (knee, ankle, elbow), the clinician can usually elicit with careful questioning the history of an initial phase of migratory polyarthralgia. This monoarticular type of disease is a true arthritis. In most pyogenic arthritides, polyarthritis is rare. Once acute rheumatic fever has been excluded, the combination of polyarticular involvement, a lack of response to salicylates, fever, and joint swelling during pregnancy should be regarded as gonococcal arthritis.

In untreated septic monoarthritis due to *N. gonorrhoeae*, the clinician may find roentgenographic evidence of joint destruction. Before the introduction of antimicrobial agents, 23% of patients who recovered from gonococcal arthritis had residual joint damage. In rare instances of untreated gonococcal arthritis, osteomyelitis may develop in the contiguous bony structure. In general, with adequate therapy, resolution of either form is prompt and complete.

The diagnosis of gonococcal arthritis is often inferred rather than documented. A definitive diagnosis may be achieved by culturing joint fluid and blood on appropriate media. When joint fluid is available, *N. gonorrhoeae* can be demonstrated by direct immunofluorescence staining. Rarely, an exudative pharyngitis with subsequent recovery of *N. gonorrhoeae* may indicate the portal of infection. In most cases the diagnosis is inferred from the recovery of the gonococcus from the endocervix or the anorectal area, and the dramatic clinical response to penicillin. Failure to achieve a dramatic response in 24 hours calls for a re-evaluation of the working diagnosis. The strains of *N. gonorrhoeae* which cause disseminated infection are highly sensitive to penicillin. Prompt clinical amelioration has been achieved with both a low-dose regimen (procaine penicillin G, 600000 units IM, given every 12 hours for up to 10 days) or a high-dose regimen of intravenous aqueous penicillin G, 10 million units daily for three days.

Gonococcal endocarditis

In the preantibiotic era, 11–26% of all endocarditis was due to *N. gonorrhoeae.* The prevalence of gonococcal endocarditis has markedly declined in contrast to the increased incidence of the arthritis-cutaneous variant of disseminated gonococcal infection. During the second and third trimesters of pregnancy, despite the relatively high incidence of disseminated gonococcal infection, there is not a concomitant increase in gonococcal endocarditis. Preliminary data have suggested that the more penicillin-sensitive strains of *N. gonorrhoeae* are more apt to produce clinical infections of the uterus and fallopian tubes or disseminated systemic disease than the more penicillin-resistant strains. In many instances, valvular involvement is aborted by relatively minimal therapy.

The majority of patients with gonococcal endocarditis experience a migratory polyarthritis which usually precedes the signs of endocarditis. Weakness, high fever, chills, and rigors with diaphoresis are characteristic presenting complaints. Symptoms reputed to be unique to gonococcal endocarditis are the double-quotidian febrile spikes (two marked spikes in the same day) and concomitant jaundice secondary to hepatic involvement. These were not uncommonly seen in the preantibiotic era. Focal embolic manifestations involving the skin, conjunctiva, kidneys, lungs, and brain usually occur when one is dealing with well-established disease. The aortic, mitral, or pulmonary valve may be involved, in order of diminishing frequency. Right-sided valvular involvement is frequently silent until perforation occurs. The site of valvular involvement dictates whether systolic or diastolic murmurs are present. The most common electrocardiographic change is a bundle-branch block (usually right) or evidence of focal myocardial injury.

The diagnosis is readily established by the recovery of the organisms from the intravascular compartment. When done during the investigation of a fever of unknown etiology (FUO), liver biopsy may reveal leukocytes within the spaces of Disse with focal parenchymal necrosis. A presumptive diagnosis is based on the signs of progressive involvement of the cardiac valves in a patient with gonococcemia. Agglutinating antibodies to *N. gonorrhoeae* develop and titers may be of diagnostic significance.

There are no set ground rules governing dosage or duration of therapy. Like *Streptococcus pneumoniae* and *Staphylococcus aureus*, *N. gonorrhoeae* produces an acute destructive process. Twenty million units of penicillin G per day by IV infusion followed by three weeks of oral ampicillin has been the regimen advocated. Current therapy is governed by the isolate's sensitivity profile to antibiotics.

In the preantibiotic era, the interim between initial manifestation and death was in the order of 10 weeks. Persistent heart failure or the presence of the murmurs of aortic insufficiency are strong indications for cardiac catheterization even in the absence of increasing left ventricular dilation and a wide pulse pressure. In our experience, successful treatment often necessitates valvular replacement. The failure of the temperature to normalize to its diurnal variation is often an antecedent to cardiac perforation.

Gonococcal chorioamnionitis and endometritis

Involvement of the fetal membranes and the subsequent clinical manifestation is the consequence of ascending gonococcal infection from glandular sites of bacterial replication. The status of the fetal membranes appears to be the major determinant of the pattern of ensuing maternal febrile morbidity. Dissolution of membrane integrity, in excess of 24 hours, may result in maternal pyrexia antenatally or in the immediate postpartum period. Examination of the placenta reveals morphologic evidence of an inflammatory process with varying degrees of vasculitis. The gonococcus is usually readily recoverable from the fetal or maternal surfaces of the placenta and from neonatal gastric aspirates. When the membranes have been ruptured for less than 24 hours, a more variable pattern in the timing of maternal disease is observed. While pyrexia still may occur in the immediate postpartum period, the infectious morbidity frequently develops

in the ensuing 24 hours. Not all patients with gonococcal endocervitis at parturition develop the postpartum endometritis.

In some patients, the clinical evidence of an endometritis does not develop until 4 to 20 days following delivery. This pattern tends to be more prevalent when the membranes are ruptured in the immediate antepartum period or at the time of parturition *per se*.

Gonococcal ophthalmia neonatorum

Before the introduction by Credé of silver nitrate, *N. gonorrhoeae* was reputed to be responsible for 12% of all blindness in the world. Gonococcal ophthalmia neonatorum is a consequence of the delivery of a neonate through an infected birth canal or its involvement *in utero* by *N. gonorrhoeae* following premature rupture of the membranes and ascending infection. Infection established before birth in this way is less likely to be aborted by silver nitrate than infection acquired during delivery.

Topical solutions of 1% silver nitrate, oxytetracycline, or erythromycin have been efficacious. An increase in the incidence of endocervical gonorrhea has engendered a proportionate increase in the number of cases of neonatal gonococcal ophthalmitis. Most of these cases occurred despite chemical or antibiotic prophylaxis. Periorbital edema and the tendency to resist manual opening of the eye on the part of the neonate contribute significantly to the problem of gonococcal ophthalmia neonatorum despite prophylaxis. The instillation of 1 % silver nitrate may result in a chemical conjunctivitis requiring smear and cultures, but this is a small price to pay compared to acute gonococcal ophthalmitis. The silver nitrate should not be subsequently rinsed out with either saline or distilled water. A saline rinse following instillation of silver nitrate decreases the probability of efficacy. In addition to the diluent effect, the cation is precipitated by the use of the saline rinse, forming silver chloride. The chemical conjunctivitis from 1% silver nitrate is a self-limited entity. Any conjunctivitis present after 24 hours should be viewed with great suspicion. Gram-staining is important in early diagnosis. In addition to *N. gonorrhoeae, H. influenzae, L. monocytogenes,* and probably *S. pneumoniae* are all capable of producing a bacterial conjunctivitis. In the case of *L. monocytogenes* (a small Gram-positive bacillus), one is dealing with a bacterial pathogen that is potentially lethal for the neonate.

The initial conjunctivitis of *N. gonorrhoeae* rapidly involves all of the contiguous portions of the eye. The resulting damage from healing by fibrosis may leave the neonate partially or completely blind. In the 1930s, isolated reports demonstrated the possible nosocomial spread of ocular gonococcal infection within newborn nurseries. This has not been a problem in the antibiotic era.

Any adequate prevention program must include not only silver nitrate prophylaxis but early identification of infected women in the course of prenatal care and the eradication of maternal infection. It is imperative to treat sexual consorts to prevent reinfection. If gravidas are treated for bacteriologically documented gonorrhea during gestation but their consorts are not aggressively sought out and treated, approximately 30% will again harbor the organism at the time of parturition.

Prepubescent gonococcal vulvovaginitis

Neisseria gonorrhoeae is one of the classic causes of vulvovaginitis in prepubescent girls. The anatomicophysiologic environment of the prepubescent vagina is ideal for the growth of the organism. The vaginal pH varies between 7 and 8 and is more conducive to gonococcal replication than the more acid adult vagina. Similarly, the absence of an estrogenic effect on the vaginal mucosa facilitates the establishment of infection.

Although gonorrhea is spread primarily by sexual congress, this is not the sole means of dissemination. Gonococcal vulvovaginitis occurs in epidemic forms, particularly in institutions with young girls. Some of these infections are probably transmitted by towels, common use of bathtubs, or the hands of infected individuals. Gonococcal vulvovaginitis readily responds to routine therapy.

Although gonococcal vulvovaginitis will occur given the opportunity, acute gonococcal salpingitis in prepubescent girls is rare. The failure of the disease to involve the endometrium and fallopian tubes is primarily a function of the anatomic status of the cervix in children. The preadolescent cervix exhibits a cryptiform configuration and has been shown to be impermeable to high intravaginal fluid under pressure. The endocervical glands are at best rudimentary.

Gonococcal pharyngitis

Changes in sexual behavior during pregnancy may include fellatio, with the result that the pharynx becomes a substantial reservoir of infection.

Gonococcal pharyngitis is seen primarily but not exclusively in patients who practice fellatio. Except following dental extraction, the gingiva, buccal mucosa, and tongue appear to be resistant to gonococcal infection. Gonococcal infection of the pharynx does not always produce clinical symptoms. When present, the most common clinical manifestation is an acute exudative pharyngitis; a less frequent presentation is chronic recurrent tonsillitis or pharyngitis. In approximately 15% of cases, asymptomatic pharyngeal infection has been the source of disseminated gonococcal infection (DGI).

Recovery of a Gram-negative, catalase-positive diplococcus from the oropharynx is not sufficient to establish the diagnosis of gonorrhea. Because of the presence of other *Neisseria* species within the microbiologic flora of the oropharynx, confirmatory fermentation tests must be performed. When selecting sites for culture for *N. gonorrhoeae* in pregnant women, one should remember that the pharynx is a more common site of infection than the anorectal region. Pharyngeal gonococcal infection is more difficult to eradicate than infection of Skene's glands or the endocervical or anorectal glands. Tests of cure in women who practice fellatio should include follow-up cultures of the oropharynx.

Gonococcal perihepatitis (Stajano-Curtis-Fitz-Hugh syndrome)

Though originally described by Stajano in 1920, gonococcal perihepatitis was not perceived as a distinct entity until the early 1930s. In 1930, Curtis conceptually linked the association of 'violin-string' or banded adhesions between the anterior surface of the liver

and the parietal peritoneum with coexistent evidence of inflammatory disease of the pelvis. He believed that these adhesions were indicative of a previous gonococcal salpingitis and cites his discussions with other physicians who had observed 'hepatic flexure colitis', pleurisy, or gallbladder pain in female patients with gonorrhea. Fitz-Hugh characterized the acute clinical presentation of what Curtis had observed in end-stage. He described three young women with pain in the right upper quadrant. One of them had been explored surgically for what was presumed to be cholecystitis. On the next day, recalling the article of Curtis, Fitz-Hugh re-examined the woman and was able to demonstrate, by Gram-staining, the presence of Gram-negative intracellular diplococci in a smear of the wound drainage.

The syndrome is quite protean in its clinical manifestations. If not aware of its occurrence, the physician may be seduced into performing an exploratory laparotomy for what is a medical disease. Not infrequently, the presence of right upper quadrant pain may overshadow an antecedent history of bilateral lower quadrant pain. Failure to perform an adequate pelvic examination coupled with a lack of appreciation of the sequential pattern of pain precludes preoperative diagnosis of this entity.

There are two basic variants: the suprahepatic (phrenic) syndrome and the infrahepatic (subcostal) syndrome of Stajano. In the suprahepatic variant, gonococcal involvement may produce, in addition to fever and pain in the right upper quadrant, right supraclavicular pain which is characteristic of rupture viscus. The infrahepatic form may produce symptoms and physical findings almost indistinguishable from those of acute cholecystitis, with a more or less localized point tenderness and pain referral along the 12th rib to the back. Roentgenograms may reveal elevation of the right hemidiaphragm. The patient experiences nausea without vomiting. The diagnosis is established by a positive smear or culture of *N. gonorrhoeae* from the cervix, prompt relief of symptoms with the appropriate antibiotic regimen, and a subsequent negative cholecystogram.

Care must be taken to distinguish this perihepatitis from the gonococcal hepatitis which can be seen in the course of disseminated gonococcal infection. In patients with DGI, an acute inflammatory infiltrate involving predominantly portal areas can be demonstrated by liver biopsies. Isolated neutrophils can be identified within the sinusoidal spaces. The pathogenesis of these two entities is sufficiently divergent to warrant a clear-cut distinction.

DIAGNOSIS

The presence of intracellular Gram-negative kidney-shaped diplococci within polymorphic neutrophils from an appropriate source is virtually pathognomonic of *N. gonorrhoeae;* nevertheless, the value of the Gram smear is limited compared to the cultural method of detecting *N. gonorrhoeae*. Comparative studies, using modified Thayer-Martin selective medium versus the Gram smear, clearly demonstrate the greater sensitivity of the cultural method. The Gram smear is used primarily as an important adjunct to cultural methods for the early diagnosis of gonorrhea in women. Since roughly one-half of all women with gonorrhea have concomitant infection in the anorectal area, when cultures are indicated samples for culturing should not be restricted to the endocervix. Obtaining an anorectal culture becomes even more imperative:

(1) when attempting to document causality in cases of presumed gonococcal arthritis; and
(2) for documentation in cases of rape.

The gonococcus is such a fastidious organism that unless properly handled it quickly dies after removal from the body. Isolation of *N. gonorrhoeae* requires a media which:

(1) contains all its complex growth requirements;
(2) contains starch or other substances which absorb inhibitory fatty acids; and
(3) contains antimicrobial agents which inhibit most non-pathogens, *Neisseria* and other species.

Because all selective media contain vancomycin, some isolates of *N. gonorrhoeae* sensitive to this antibiotic will go undetected.

The microbiological diagnosis of *N. gonorrhoeae* is based on:

(1) characteristic colony appearance;
(2) Gram-stain characteristics (Gram-negative diplococci);
(3) demonstration of oxidase positivity; and
(4) selected sugar utilization or immunofluorescent confirmation.

To obtain superior isolation results, ground rules need to be followed:

(1) Never culture a sample on a plate that is not at least at room temperature. *Neisseria gonorrhoeae* has an extremely limited thermal tolerance. Preferential growth occurs between 30º and 36ºC. Temperatures below room temperature will rarely sustain the replication of *N. gonorrhoeae* and often account for non-recovery of the organism.
(2) Incubate cultures immediately. *N. gonorrhoeae* does not tolerate drying. Again the thermal liability of the organism is such that maintaining cultures at room temperature for more than one hour is destined to have a deleterious effect. One can almost establish a linear decay curve between recovery of organisms and prolonged exposure at suboptimal temperatures. If transport to a diagnostic laboratory is required, when possible, incubate the culture 6–10 hours before attempting transport.
(3) Be sure to provide a source of carbon dioxide. In dealing with the Thayer-Martin plates, it is imperative that they not only be incubated, but that candle jars be utilized to provide the critical 5% CO_2 atmosphere required for the initiation of bacterial replication. Unless an extremely heavy inoculum of the bacteria is present, the likelihood of successfully culturing the organism is markedly reduced. With the Transgrow bottles, think of the CO_2 as liquid and handle those bottles in a comparable way. They should never be inverted. The Neigon (JEM-BEC) system contains its own CO_2-generating capacity such that the initial use of candle jars is less critical.
(4) Probably the single greatest failure is that of a physician not rolling the swab in a Z or W manner. The swab when placed within the endocervical canal samples 360º; yet if one does not roll the swab, a maximum of 33–40% of the swab is sampled. One hundred percent sampling is exceedingly important when dealing with a situation where *N. gonorrhoeae* is present in quantities that are numerically reduced (e.g. the asymptomatic carrier or the patient with initial gonococcal salpingitis who is now undergoing a facultative anaerobic superinfection at the endocervix).

A single culture from the endocervix plated on selective media and handled under near optimal conditions has a sensitivity of 84–89%.

The culture prerequisite for pre-heated culture plates, ambient CO_2, selective media, and marked organismal thermal liability has resulted in a gross under-diagnosing of subclinical infection.

With current methodology, in many institutions less than one-third of all subclinical carriers of gonorrhoeae are identified by bacterial cultures. The development of DNA probes complementary to ribosomal RNA of *N. gonorrhoeae* is an important diagnostic advance.

DNA probes will be of great benefit for patient clinic facilities which must rely on off-site laboratories. The value of DNA probes is that:

(1) they allow for concomitant testing of *Chlamydia trachomatis*,
(2) specimens can be frozen indefinitely and retested at a later date, if needed; and
(3) they offer markedly superior sensitivity over suboptimally handled endocervical specimens.

The short-comings of the probes are that they:

(1) are currently approved only for endocervical and urethral specimens. Test of cure may require anorectal or pharygneal specimens; and
(2) cannot be used to identify antibiotic-resistance pattern of a given gonococcal isolate.

The sensitivity of the DNA probes will be enhanced when the polymerase chain reaction (PCR) or ligase chain reaction (LCR) tests become the standard technology used for the diagnosis.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance in the gonococcus can be plasmid mediated, chromosomally mediated, or both. In the United States, many variations have been identified. The three most important, from a public health standpoint, are plasmid-mediated resistance to penicillin (PPNG); chromosomally-mediated resistance to penicillin (CMRNG); and plasmid-mediated, high-level tetracycline resistance (TRNG).

PPNG: PPNG are gonococcal strains that have acquired an extrachromosomal element or plasmid that encodes for beta-lactamase, an enzyme that destroys the betalactam ring of penicillin. Of the resistant strains, PPNG has had the greatest impact on public health programs and resources in the mid-1980s.

CMRNG: Unlike strains of plasmid-mediated resistance, strains with chromosomal resistance to penicillin do not produce beta-lactamase. Chromosomally-mediated resistance is not limited to penicillin, but is a more general phenomenon that can include resistance to tetracycline, the cephalosporins, spectinomycin, and other aminoglycosides. In most instances to date, those strains have not been associated with treatment failure, either because the levels of resistance have been high or because the antibiotic in question was not used for therapy.

TRNG: Gonococcal isolates with plasmid-mediated, high-level resistance to tetracycline (minimal inhibitory concentration>16 mg/ml) were first identified in 1985.

Although many individual cases and clusters of TRNG have since been reported, investigation has shown that in most instances, CDC treatment guidelines were followed regarding dual therapy with penicillin and tetracycline, thus avoiding therapy failure. For nearly all patients with TRNG who have been treated with tetracycline alone, the therapy has not been effective.

Quinolone resistant *N. gonorrhoeae* (QRNG): Cases of gonorrhea caused by *N. gonorrhoeae* resistant to fluoroquinolones have been reported sporadically from many parts of the world, including North America.

Quinolone resistant *N. gonorrhoeae* is widespread in parts of Asia and the Pacific. In the united States, QRNG is becoming increasingly common on the West Coast. Because of the progressive dissemination of QRNG, quinolones are no longer recommended for the treatment of gonorrhea in the states of Alaska, Hawaii and California and should not be used in the treatment of infection that may have been acquired in Asia and the Pacific.

Gonococcal organisms with decreased *in vitro* susceptibilities to ciprofloxacin have deceased susceptibilities to all fluoroquinolones, including ofloxacin, enoxacin, iomefloxacin, and norfloxacin. Importation of QRNG is likely to continue. The dissemination of QRNG in the United States may well increase to a point when fluoroquinolones can no longer be relied upon to eradicate gonoccal infections.

THERAPY

In terms of specific antibiotic therapy, the form of gonococcal disease dictates its therapy. The CDC 2002 guidelines for treatment of gonococcal infection in the United States take into account several observations: the high frequency of coexisting chlamydial and gonococcal infections, increased recognition of the serious complications of chlamydial and gonococcal infections, the difficulty in diagnosing chlamydial infection, the increasing incidence of infections due to both plasmidmediated (PPNG) and chromosomally-mediated resistant *N. gonorrhoeae* (CMRNG), and published reports of the emergence of tetracycline-resistant gonococci in some geographic areas (Table 26.1).

Women and men exposed to gonorrhea (e.g. within the past 60 days) should be examined, cultured, and treated prophylactically with one of the regimens which covers both gonococcal and chlamydial infections.

Meningitis and endocarditis

Patients with gonococcal meningitis or endocarditis occurring in PPNG-endemic and hyperendemic areas should be treated with high-dose intravenous third generation cephalosporins in consultation with an expert. Optimal therapy may be guided by results from *in vitro* susceptibility tests. Most authorities recommend treating patients with meningitis for 10–14 days and those with endocarditis for at least one month.

Ophthalmia

In PPNG-endemic and -hyperendemic areas, adult patients with gonococcal ophthalmia should be hospitalized and treated with either ceftriaxone, 1 g, once a day, IM or IV, for 5

days, or with equivalent doses of another effective third generation cephalosporin. An ophthalmologist should evaluate the patient for ocular complications. Adjuvant topical antibiotics are not thought to offer any significant advantage. Irrigation of the eyes with saline or buffered ophthalmic solutions may be useful adjunctive therapy to eliminate discharge.

Gonococcal ophthalmia in neonates

Untreated gonococcal ophthalmia in neonates is highly contagious and may rapidly lead to blindness. All neonates with gonococcal ophthalmia in PPNG-endemic and hyperendemic areas should be treated with ceftriaxone, 25–50 mg/kg body weight/day, IV or IM, for 7 days. An equivalent third-generation cephalosporin may be used in appropriate doses. Topical antimicrobial preparations alone are not sufficient and are not required when appropriate systemic therapy is given. Irrigation of the eyes with saline or buffered ophthalmic solutions may be useful adjunctive therapy to eliminate discharge. Both parents of newborns with gonococcal ophthalmia must be treated. Simultaneous ophthalmia infection with *Chlamydia trachomatis* has been reported and should be considered if a patient does not respond satisfactorily to recommended treatment.

Table 26.1 2002 CDC therapeutic recommendations for gonoccal infections

Uncomplicated gonococcal infections of the cervix, urethra, and rectum	**Alternate regimens**
Recommended regimens	Cefotaxime 1 g IV every 8 hours **OR** Ceftizoxime 1 g IV every 8 hours **OR** *For persons allergic* to *ß-lactam drugs:* Septinomycin 2 g IM every 12 hours. All regimens should be continued for 24–48 hours after improvement begins; then therapy may be switched to one of the following regimens to complete a full week of antimicrobial therapy: Cefixime 400 mg orally 2 times a day **OR** (Ciprofloxacin 500 mg orally 2 times a day) **OR** (Ofloxacin 400 mg orally twice a day) **OR** (Levofloxacin 500 mg orally daily)
Cefixime 400 mg orally in a single dose **OR** Ceftriaxone 125 mg IM in a single dose **OR** Ofloxacin* 400 mg orally in a single dose **OR** Ciprofloxacin* 500 mg orally in a single dose/ **OR** Levofloxacin* 250 mg orally in a single dose **PLUS** (if chlamydial infection is not ruled out) Doxycycline 100 mg orally twice a day for 7 days **OR** Azithromycin 1 g orally in a single dose	**Opthalmia neonatorum caused by *N. Gonorrhoeae***
Alternate regimens	**Recommended regimen**
Spectimomycin 2 g in a single IM dose Single-dose cephalosporins (ceftizoxime 500 mg IM; ceftriazone 500 mg 1M	Ceftriaxone 25–50 mg/kg IV or IM in
Uncomplicated gonoccal infections of the pharynx	
Recommended regimens	

Ceftriaxone 125 mg IM in a single dose **OR**
Ciprofloxacin 500 mg IM in a single dose **PLUS** (if chlamydial infection is not ruled out)
Azithromycin 1 g orally in a single dose **OR**
Doxycycline 100 mg orally 2 times a day for 7 days or another regimen effective against *C. trachomatis*

Quinolones should not be used for infections acquired in Asia or the Pacific including Hawaii. The use of quinolones is probably inadvisible for the treatment of disease acquired in California and in other areas with increased prevalence of quinolone resistance

Pregnant women should not be treated with quinolones or tetracyclines. Gravida infected with *N. gonorrhoeae* should be treated with a recommended or alternate cephalosporin.Women who can tolerate a cephalosporin should be administered a single dose of 2 g of spectinomycin IM

Disseminated gonoccal infection

Recommended regimen

Ceftriaxone 1 g IM or IV every 24 hours

single dose, not to exceed 125 mg
Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered.

Prophylactic treatment for infants whose mothers have gonoccal infection

Infants born to mothers who have untreated gonorrhea are at high-risk for infection.

Recommended regimen in the absence of signs of gonoccal infection

Ceftriaxone 25–50 mg/kg IV or IM, not to exceed 125 mg, in a single dose
Mother and Infant should be tested for chlamydial infection.
Azithromycin 2 g PO is effective against uncomplicated gonoccal infection but it is expensive and too often causes gastrointestinal distress to be used except for in special situations.

MANAGEMENT OF SEX PARTNERS

Patients should be instructed to refer sex partners for evaluation and treatment. All sex partners of patients who have *N. gonorrhoeae* infection should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last sexual contact with the patient was within 60 days of onset of the patient's symptoms or diagnosis. If a patient's last sexual intercourse was more than 60 days before symptom onset or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to avoid sexual intercourse until therapy is completed and patient and partner(s) are without symptoms.

NEONATAL PROPHYLAXIS AND PROPHYLACTIC TREATMENT

All newborns should receive ocular prophylaxis with either 1% silver nitrate solution, 1% tetracycline solution (or ointment), or 0.5% erythromycin ointment. Prophylaxis should be given within 1 hour after birth. No one regimen is completely effective. Tetracycline and erythromycin are also active against *C. trachomatis*. The prophylaxis failure rate of the antibiotic preparations for infections with resistant gonococcal strains is unknown. However, the intraocular antibiotic concentrations achieved with routine prophylaxis are high.

Neonates born to mothers with documented gonococcal infection peripartum should be treated with ceftriaxone 125 mg, IM, in one dose. Low-birthweight infants should receive 25–50 mg/kg body weight.

TREATMENT FAILURES

If gonorrhea persists after treatment with one of the non-spectinomycin regimens, patients should be treated with spectinomycin 2.0 g IM. Recurrent gonococcal infections after treatment with the recommended schedules commonly are due to reinfection rather than treatment failure and indicate a need for improved sexpartner tracing and patient education. Since antimicrobial resistance is a cause of treatment failure, all post-treatment isolates should be tested for antimicrobial susceptibility.

RECOMMENDATIONS FOR THERAPY OF CONCOMITANT SYPHILIS

The concept that gonorrhea was a manifestation of syphilis resulted from John Hunter's experiment in 1767 of self-inoculation of pus from the urethra of an individual supposedly infected with gonorrhea. It was not until 1873 that Benjamin Bell clearly demonstrated that gonorrhea and syphilis were two separate disease entities. Nevertheless, this unfortunate experiment in self-inoculation serves to stress the fact that in approximately 1–2% of cases of gonorrhea there is a concomitant infection with *Treponema pallidum*. Evidence of possible concomitant infection must be actively sought. The therapy for syphilis is inadequate for the treatment of gonorrhea, and vice versa.

Although long-acting forms of penicillin (such as benzathine penicillin G) are effective in the treatment of syphilis, they have no place in the treatment of gonorrhea. Penicillin preparations and cephalosporins not recommended for the treatment of gonorrhea include benzathine penicillin G, oral penicillin G, penicillin V, cloxacillin, dicloxacillin, cephradine, cephalothin, cephapirin, cefazolin, cephalexin, cefadroxil, and cefaclor.

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27
Salmonella typhi

The salmonellae are short plump rods which occur singly in pairs or in chains. The organisms stain Gram-negative and are actively motile. All known *Salmonella* species are pathogenic for man and domesticated animals. Isolates that fulfill the selected biochemical prerequisites of the genus fall into three groups: *typhi, cholerae suis, and enteritidis*. Subclassification is achieved by serologic segregation based on the somatic (O) and flagella (H) antigens. More than 1400 serotypes have thus been identified; however, just 11 serotypes account for approximately 60–70% of human isolates. These include *S. enteritidis*, serotypes *typhimurium, enteritidis, copenhagen, newport, heidelberg, infantis, thompson, blockley, dergy* and *S. typhi*.

PATHOGENESIS

The portal of infection is almost invariably the gastrointestinal tract. The ability to infect man is primarily a quantum-related phenomenon. *Salmonella typhi*, in small doses, may be rapidly eliminated, except when there has been an alteration of the acid barrier, as may occur in patients with partial gastrectomy, where as little as 10 organisms of *Shigella* may produce disease. An infective dose of 10^5 organisms or greater is required to produce salmonellosis.

A second important host defense mechanism is bacterial flora of the gastrointestinal tract which exerts a strong hemostatic influence. Many anaerobes produce short chain fatty acids which are postulated to inhibit the growth of viral and bacterial enteric pathogens. Alteration of the enteric flora with antibiotic therapy increases susceptibility of experimental animals and man to enteric pathogens. Gastric acid buffering with antacids or compromising gastric function by disease or prior surgery may alter susceptibility. Patients with achlorhydria have been shown to have higher incidences of acute diarrheal disease.

A final factor potentially contributing to the induction of disease is the fact that selected strains of *S. typhi* possess a Vi surface antigen which may interfere with the bactericidal activity of serum and phagocytosis. *S. typhi* tends to elicit a predominantly mononuclear inflammatory response. Non-typhoid salmonellae lead to a predominantly polymorphic response.

The salmonellae characteristically invade the intestinal epithelium; however, extensive destruction of the intestinal mucosa does not occur. The lining epithelium is left relatively intact. A significant inflammatory exudative response is elicited in the lamina propria. Disease at this site has the potential to lead to septicemia.

With penetration of the bacteria through the intestinal mucosa, dissemination is initially by lymphatics to the regional nodes and ultimately by the intravascular compartment. *S. typhi* is one of the bacteria of man which has a predilection for the reticuloendothelial system (RES). The initial bacteremia is rapidly cleared by the reticuloendothelial cells in the liver, spleen, and bone marrow. While the liver, spleen,

and mesenteric nodes are all enlarged as a consequence of hypertrophy of the RES, only splenic enlargement is commonly observed clinically. Bacterial replication occurs within these intracellular sites. The relative protection from host defense mechanisms afforded by the intracellular sites of replication accounts for the persistence of the bacteria. Clinical disease becomes manifest when the bacteria re-enter the vascular compartment from their intracellular sites of replication. The latent stage between ingestion and overt disease is usually of the order of 8 to 14 days but may range from 3 to 60 days. During this phase, the biliary tract becomes infected. The multiplication of typhoid bacilli in the bile leads to secondary seeding of the gastrointestinal tract and accounts for the increased number of *S. typhi* observed in the feces during the second and third weeks of clinical illness. Involvement of the lymphoid tissue in the intestinal tract, particularly the Peyer's patches in the terminal ileum, may be responsible for the subsequent diarrhea state, which is often associated with hemorrhage, and on rare occasions may cause ileal perforation.

Immunity to *S. typhi* is not related to the presence of specific antibodies. There is no correlation between resistance to infection, recurrence, or relapse and the titer of antibodies to O, H, or Vi antigens of the typhoid bacillus. Resistance is presumably a function of cell-mediated immunity at the RES level.

All *Salmonella* serotypes are capable of producing a septicemia or typhoid-like picture. A transient bacteremia may be the rule rather than the exception in symptomatic *Salmonella* infections. The younger the patient, the greater the probability of documented septicemia. Infants with *Salmonella* gastroenteritis under 90 days of age appear to be at greater risk for developing invasive disease. The frequency of nosocomial epidemics suggests that the infecting dose in newborns is considerably less than the 10^5 organisms usually needed to infect adults.

Mortality following *Salmonella* bacteremia is low compared with other Enterobacteriaceae. Of those with clinically overt bacteremia, fewer than 10% will develop severe life-threatening sepsis or metastatic infections. If there is an underlying disease process, such as malnutrition, the ensuing mortality or the incidence of serious sequelae is significantly increased.

Metastatic infected foci may not be apparent at the time of initial clinical presentation, and osteomyelitis, for example, may manifest during or after initial therapy (Table 27.1).

Meningitis is almost exclusively a disease entity of children under one year of age. Even with optimum support, the results of therapy tend to be poor. The overall mortality is 60%. Morbidity, due to ventriculitis, subdural empyema, hydrocephalus and chronic neurologic defects, is unfortunately common.

A sustained bacteremia in a gravid female introduces the possibility for transplacental infection and congenitally acquired disease.

Table 27.1 Metastatic infectious complications of Invasive *Salmonella* septicemia

Meningitis	Osteomyelitis
Pneumonia	Septic arthritis

FETAL INVOLVEMENT

Having fulfilled the major prerequisite, namely the ability to mount a sustained bacteremia, the salmonellae have the potential to traverse the placental barrier and produce infection within the developing fetus. Involvement appears to be a two-step phenomenon in which the fetus is not affected until infection is established within the placenta and subsequent invasion of the fetal vascular compartment occurs. Pregnancy does not alter the maternal prognosis; however, the disease has a major effect on perinatal morbidity. An increased incidence of abortion or prematurity is observed when typhoid fever is superimposed on pregnancy. Much of the fetal mortality reported in the literature is secondary to the severity of maternal disease, rather than intrauterine involvement. When fetal exposure to maternal disease has been less than two or three weeks in duration, the typhoid bacillus has not been isolated at autopsy from the spleen, bone marrow, or liver of fetuses who have been aborted. This observation theoretically supports the contention that fetal involvement is a two-step phenomenon and the probability that early perinatal mortality and morbidity are due to the consequences of maternal disease; later in the course of the disease, fetal colonization and fetal infection may occur. In the majority of instances, even though the same strain of *S. typhi* is recovered from the alimentary tract of the newborn infant, the child is asymptomatic. The possibility that these isolates from the neonate were acquired during parturition as a consequence of delivery through an infected birth canal is unlikely. Fecal cultures are usually negative for *S. typhi* during the incubation period. Fetal involvement during the convalescent phase of the maternal disease carries with it a surprisingly good prognosis. Dildy *et al.* reported on a woman convalescing from typhoid fever who gave birth to a child with evidence of intrauterine dissemination. This child was isolated from the mother in the immediate postpartum period, yet *S. typhi* was repeatedly cultured from stools and a high titer of O and H typhoid agglutinins were demonstrable in the cord blood. A similar case was reported by Wing and Troppoli. Again the mother was convalescing from typhoid fever and gave birth to a child who had *S. typhi* in the feces and whose cord serum gave a positive Widal reaction. The Widal reaction is contingent on IgM antibodies. Since neither IgM nor IgA antibodies traverse the placental barrier, the presence of such agglutinins in cord blood indicates intrauterine exposure.

Awadalla *et al.* reported a case of a primagravida who at 26 weeks gestation developed a severe *S. typhi* gastroenteritis, sepsis and disseminated intravascular coagulopathy. Shortly after the institution of antibiotic therapy, she spontaneously aborted a previable infant from whose intact gestational sac was recovered *S. typhi*. The amniotic fluid was grossly turbid.

The asymptomatic congenitally infected neonate as well as individuals with rectal carriage are the potential reservoirs for nosocomial salmonellosis in newborn intensive care nurseries.

In utero dissemination of maternal salmonella infection is not restricted to *S. typhi*. *Salmonella enteritidis* can occasionally access the fetus *in utero*. Any *Salmonella* serotype producing a bacteremia lasting days to weeks can be responsible for induction of fetal infection/disease.

FEMALE GENITAL TRACT INVOLVEMENT

Heamatogenous dissemination to the ovary has been reported. In a review of 8000 cases of salmonellosis, Cohen *et al.* identified 9 cases of an ovarian abscess. Disease manifests as an acute abdomen with fever, abdominal pain, and a unilateral mass. Almost invariably, an abscess occurred in an ovary with some sort of pre-existing lesion including simple cyst, dermoid, endometrioma, and cystadenoma. The corresponding fallopian tube is relatively free of disease.

DIAGNOSIS

Clinical presentations

The non-typhoidal cases of salmonellosis usually present as acute-onset diarrhea in pregnancy. An unexplained

Table 27.2 Common signs and symptoms of typhoid fever

Persistent fever
Abdominal pain
Diarrhea
Hypothermic response to antipyretics
Headache
Splenomegaly
Rose spots (small petechial hemorrhages)
Generalized malaise
Chills
Relative bradycardia
Relative leukopenia

splenomegaly in association with a relative lymphocytosis may be present.

In typhoidal-like disease (Table 27.2), once patients enter the septicemic stage, they commonly suffer from head pain, sore throat, chills, and persistent fever. The white blood cell count tends to be depressed and is often under 5000/mm^2 with a marked shift to the right. What is impressive is the marked temperature-pulse dissociation. The patient tends to have a bradycardia which is disproportionate to the temperature. There are a number of cutaneous manifestations associated with the disease, varying from ‘rose spots’ to transient erythematous maculopapular rashes. Once the organisms have reappeared in the stool, diarrhea, which may be bloody, is not uncommon. In rare instances, the patient may experience ileal perforation.

Salmonellosis is a disease of the small bowel. Careful history is helpful in distinguishing small bowel versus large bowel disease. The occurrence of large watery or bulky stools suggests a small bowel origin. The presence of rectal pain and urgency to defecate is characteristic of large bowel disease. The colicky pain of small bowel disease tends to be periumbilical in distribution whereas terminal ileum and large bowel pain is referred to areas clearly below the umbilicus.

A second procedure which should be done in evaluating the significance of potentially infectious diarrhea in a gravid female is examination of stool for fecal leukocytes. The absence of fecal leukocytes depends on the integrity of the intestinal mucosa. Diseases which inflame or disrupt the intestinal mucosa frequently cause shedding of fecal leukocytes. Normal controls and diseases in which the intestinal mucosa remains relatively normal seldom cause excretion of fecal leukocytes. The demonstration of polymorphonuclear leukocytes in feces warrants the submission of feces for enteric pathogen culturing.

Procedure for detection of fecal leukocytes

Examination for fecal leukocytes is easily performed by placing a small fleck of mucus (or stool if no mucus is present) on a clean microscope slide and mixing it thoroughly with two drops of Loeffler's methylene blue stain. A coverslip is then placed over the mixture and after two to three minutes the slide is examined microscopically. Leukocyte nuclei will appear blue with this technique. Specimens should be taken from the outside of stool specimens, and not from the center or from the rectal swabs which may give false-negative stains for leukocytes.

The absence of fecal leukocytes does not exclude an enteric pathogen etiology. Those agents which produce their diarrheic effect via enterotoxins usually are not associated with the presence of fecal leukocytes. The principal exceptions are:

(1) *Shigella dysenteriae* and
(2) *Clostridium difficile.*

The ultimate diagnosis rests on recovery of a pathogenic strain of *Salmonella* from stool or blood. The following procedure is recommended.

Stool specimens for microbiological analysis

The stool sample should be fresh and warm and should be free from contamination with barium, bismuth, oils, antibiotics, antacids, or kaolin antidiarrheal agents.

The best specimen is a freshly passed stool obtained before the initiation of antimicrobial therapy. A rectal swab in a transport medium is a poor choice. Unless the specimen can be taken immediately to the laboratory and properly handled there, a number of significant microorganisms will not survive the changes in pH which occur with a drop in temperature. This is

Table 27.3 Therapeutic recommendations for nontyphoidal *Salmonella* infections

Uncomplicated enteritis in normal hosts	Antibiotics do not abbreviate period of symptoms or prolong asymptomatic excretion; however, relapse more common when antibiotics given; antibiotic therapy CONTRAINDICATED
Enteritis with bacteremia	If toxicity persists and bacteremia more than transient event, antibiotic therapy INDICATED
Colitis (characterized by fever, abdominal pain and tenesmus)	antibiotic therapy INDICATED
Metastatic complications (meningitis, osteomyelitis, septic arthritis)	antibiotic therapy INDICATED
Secretory diarrhea	Brief course of non-absorbable antibiotic such as colistin sulfate or neomycin sulfate
Immunocompromised host	Individualization of each case

especially true of most shigellae and an appreciable number of the salmonellae.

Similarly, refrigeration markedly diminishes the probability of isolating enteric pathogens. While alternative methods exist to diminish the changes in pH, the price is an increased incidence of falsely negative bacteriological cultures. If sterile swabs are used in obtaining the specimen, they should be passed beyond the anal sphincter, carefully rotated, and withdrawn.

THERAPY

Typhoidal and septicemic variants should be treated with antimicrobial drugs. The selection of initial antibiotic therapy is influenced by prior identification of resistant strains in the community.

Uncomplicated *Salmonella* gastroenteritis is usually not an indication for drug therapy *per se* unless the individual involved is at special risk (Table 27.3). Underlying conditions which would sanction antimicrobial therapy are:

Table 27.4 Antimicrobial agents for potential use in the treatment of *S. typhi* in pregnancy

Ampicillin, 8 g/day IV
Ceftriaxone, 75 mg/kg/day for 5 days
Amoxicillin, 4–6 g/day in 4 divided doses
Cefoperazone, 2 g b.i.d. IV to 4 g q.i.d.

(1) lymphoproliferative diseases;
(2) vascular grafts;
(3) aneurysms;
(4) valvular heart disease and;
(5) sickle cell-related diseases.

The current drugs of choice in non-gravida are the fluoroquinolones. Antibiotics commonly used in pregnancy are listed in Table 27.4.

In face of life-threatening disease, maternal considerations should have priority over potential fetal adverse drug reactions.

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28
Streptococcus pneumoniae

Streptococcus pneumoniae is a catalase-negative Gram-positive coccus that replicates in chains in liquid medium. Clinical isolates of *S. pneumoniae* contain an external capsule; only rarely have unencapsulated isolates been implicated as the cause of infection. Pneumococci produce a substance which breaks down hemoglobin causing a green color; as a result, pneumococcal colonies are surrounded by a green zone during growth on blood agar plates. More than 80 serotypes of *S. pneumoniae* have been identified based on antigenic differences in their capsular polysaccharides.

Streptococcus pneumoniae is not a normal constituent of vaginal bacterial flora; however, given the opportunity, *S. pneumoniae* can be a significant pathogen for the female genital tract.

Classically, involvement with the female genital tract has occurred in conjunction with primary pulmonary disease, engenderment of bacteremia, and subsequent metastatic involvement.

STREPTOCOCCUS PNEUMONIAE (PNEUMOCOCCAL) PNEUMONIA IN PREGNANCY

With the advent of antibiotics and in the absence of underlying chronic disease or acute alcoholism, death due to *S. pneumoniae* is a rarity. Yet lobar pneumonia is still associated with a 2–3% maternal mortality when significant disease occurs in pregnancy. Fetal mortality approaches 30%. Both maternal and fetal mortality and morbidity are influenced by the extent of disease and the aggressiveness of therapy Although not infrequently a history suggestive of virus-like upper respiratory infection can be elicited, the onset of disease often occurs with dramatic suddenness. The patient develops fever, cough, and malaise. The initial stage of pulmonary parenchymal involvement is characterized by marked vascular engorgement, serous exudate, and rapid bacterial proliferation. The thick, mucoid capsule of the bacterium impedes immediate phagocytosis and is responsible for the virulence of the organism. In contrast to the group A streptococci, virulence of *S. pneumoniae* is primarily a function of the organism's ability to replicate and evoke an acute inflammatory reaction, rather than one of exo- or endotoxins or extracellular enzymes. The pneumococcus is a classic example of an organism that is highly pathogenic by virtue of its replicative ability. The pneumococci are numbered from 1 to 81 in the order in which they were identified.

The cough is sequentially productive first of turbid, watery sputum, which rapidly converts to purulent and grayish green, and then assumes the characteristic rust color. The changes in the sputum parallel those within the lung parenchyma. The initial serous exudate and vascular engorgement give way to a precipitous increase in neutrophils,

extravasation of red blood cells, and precipitation of fibrin. The confluent exudative reaction tends to obscure the pulmonary architecture.

With the extension of the disease process to the pleural surfaces and the disruption of vascular elements, the patient experiences pleuritic chest pains, chills, and tremor. Shortness of breath, orthopnea, and cyanosis tend to reflect the extent to which the vital capacity of the lung parenchyma has been compromised. In pregnant women the degree of oxygen unsaturation is often greater than anticipated. On physical examination the patient exhibits a diminution of breath sounds associated with fine crepitant rales. With consolidation, increased tactile and vocal fremitus and bronchial breath sounds occur.

Prior to the advent of antibiotics, the disease usually persisted for 7–9 days. Extreme hypoxia and generalized vasomotor collapse usually led to death. In patients who ultimately recovered, a period of apparent clinical deterioration occurred about the eighth day, preceding recovery by crisis. Tachypnea and tachycardia increased, and the sensorium became obtunded. Then, precipitously, the breathing became less labored, the pulse rate dropped, and the fever lysed. Within hours the seemingly moribund patient was transformed into a convalescent patient. Fortunately, in terms of morbidity and mortality, recovery is no longer a quantitative and possibly qualitative function of antibody synthesis.

METASTATIC FETAL INVOLVEMENT

The primary deleterious consequence of severe maternal pneumonia due to *S. pneumoniae* is fetal wastage. Beyond the question of possible maternal demise, a certain component of fetal wastage is difficult to avoid, owing to a failure to curtail aggressively maternal hyperthermia.

S. pneumoniae is capable of affecting the products of conception by other hematogenous involvement or ascending infection. Either mechanism results in chorioamnionitis and/or perinatal septicemia.

FEMALE GENITAL TRACT INVOLVEMENT

Vaginal carriage of *S. pneumoniae,* when present within the vaginal flora, is a rare occurrence. The microorganism may have a higher invasion to colonization ratio than the group B streptococci. At the time of parturition or rupture of the fetal membranes, bacteria have the ability to ascend and infect the amniotic sac and secondarily the fetus.

Involvement of the female genital tract as a metastatic process secondary to maternal septicemia due to *S. pneumoniae* was a relatively well-documented phenomenon in the pre-antibiotic era.

The occurrence of cases of chorioamnionitis and/or perinatal septicemia in the absence of pulmonary involvement indicated the possibility of contiguous spread from the vaginal/cervical reservoir and subsequent involvement of the female upper genital tract. Hughes *et al.* described a case of neonatal pneumococcal sepsis in the product of a 37 week uneventful gestation. The mother simultaneously developed bacteremia with the same serotype organism and died from septic shock. DNA fingerprinting confirmed the

identicality of both isolates. Nallusamy reported two cases of invasive early-onset neonatal pneumococcal sepsis. One neonate was born with no maternal risk factors present and the other was preterm at 35 weeks. Evidence of infection was not present at parturition. Despite penicillin therapy, both neonates died. Kahike *et al.* described a case of pneumococcal peritonitis which occurred four weeks after the patient had given birth to a healthy boy. High vaginal, blood and operative cultures were all positive for *S. pneumoniae*.

Genital tract disease due to *S. pneumoniae* has been reported in non-pregnant females. Isolated cases of spontaneous pneumococcal peritonitis have been described. Hadfield *et al.* reported a case of a 46-year-old woman with bilateral tubo-ovarian masses. Biopsy specimens from both tubes and from the wall of the abscesses demonstrated Gram-positive, lancet-shaped diplococci which were documented to be *S. pneumoniae* by immunoperoxidase staining. Rahav *et al.* reported a case of postmenopausal pneumococcal tubo-ovarian abscess from which *S. pneumoniae* was recovered. The fallopian tubes in these two cases of spontaneous peritonitis due to *S. pneumoniae* in females were described as being swollen and hyperemic with pus emanating from the ends. What was described is not a specific disease entity (spontaneous peritonitis) but more probably a progressive consequence of salpingitis. Rare causes of acute salpingitis due to *S. pneumoniae* have been reported. *S. pneumoniae* appears to be able to function as a primary pathogen for the fallopian tubes. The entire pathogenic spectrum previously attributable to *Neisseria gonorrhoeae* can potentially be mimicked by *S. pneumoniae*.

DIAGNOSIS

A presumptive diagnosis is inferred from the presence of encapsulated lancet-shaped diplococci in significant numbers on a Gram-stained smear of the sputum. Immunization of rabbits stimulates the appearance of antibodies that cause serotype-specific agglutination or microscopic demonstrability of the capsule (the Quellung reaction): this reaction is due to increased visibility of the capsule because the interaction with antibody renders it retractile, not only to capsular swelling, which is often said to be responsible.

This reaction can be used for quick identification and typing of the organism. In adults, types I through VIII are responsible for about 80% of the cases of pneumococcal pneumonia, and for more than one-half of the fatalities from pneumococcal bacteremia. Ultimate confirmation of the diagnosis rests with bacteriologic identification of the organism.

Pneumococci are identified in the routine microbiology laboratory by three reactions:

(1) the so-called alpha-hemolysis of blood agar;
(2) catalase negativity; and
(3) solubility in bile salts or susceptibility to ethyl hydrocupreine (optochin). In recent years a number of isolates have been found to be optochinresistant, which has led cautious microbiologists to rely more on the use of bile solubility for definitive identification.

While *S. pneumoniae* will grow on 5–7% sheep blood agar culture when incubated in a CO_2 environment, the recovery of alpha hemolytic streptococci is usually not worked up

any further and is often reported as ‘mixed vaginal flora’. Recovery of alpha hemolytic streptococci from patients with acute salpingitis needs to be microbiologically evaluated to exclude the possibility that these isolates are *S. pneumoniae*.

THERAPY

Penicillin is the drug of choice for susceptible or intermediately resistant strains of *S. pneumoniae*. Most hospitalized patients are treated with intravenous drugs, in which case 500000–1000000 units q4h is adequate therapy. A third-generation cephalosporin is an alternative for parenteral therapy.

Resistance on the part of pneumococcal isolates to the beta-lactam antibiotics has become a major problem. The decision to add alternate drug therapy is predicated on sensitivity patterns of local *S. pneumoniae* isolates. In most cases, it is prudent to presume the existence of a resistant strain and treat accordantly with ‘best fit for spectrum’. If a bacteriostatic antibiotic is to

Table 28.1 Recommendations for pneumococcal vaccine use

Immunocompromised adults at increased risk for pneumococcal disease include those with:	
1.	chronic cardiovascular disease
2.	chronic pulmonary disease
3.	diabetes mellitus
4.	alcoholism/cirrhosis
5.	adults aged 65 or over

be used in conjunction with a bacteriocidal antibiotic, it is recommended that the bacteriocidal antibiotic be given at least one half hour before the bacteriostatic antibiotic. If the isolate is sensitive to penicillin, the ‘drug of choice’ concept applies.

PREVENTION

Pneumococcal vaccination is an important part of the pneumococcal disease prevention. In the past, uncertainty about local reactions and the duration of protection have limited the use of pneumococcal vaccination. Currently, the use of pneumococcal vaccine should be predicated on: (1) the risk to the patient population; and (2) whether a pneumococcal vaccination has been procured six years or more previously.

S. pneumoniae remains a major cause of morbidity and mortality in both developed and underdeveloped countries. To address the need for protection in infancy, maternal immunization with the newer pneumococcal vaccines has been aggressively advanced as a strategy to prevent disease during a period of increased vulnerability in infants.

The pneumococcal vaccine available before 1983 was a 14-valent pneumococcal vaccine. The currently licensed pneumococcal polysaccharide vaccine is composed of 23 capsular polysaccharide. Many of these antigens are of poor immunogenicity in infants under the age of five, but not in adults.

Patients recommended for primary or revaccination are listed in Table 28.1. Immunocompromised individuals with splenic dysfunction, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, transplantation, or hepatitis C virus have an increased risk of pneumococcal disease.

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29
Group A β-hemolytic streptococci
(Streptococcus pyogenes)

The group A beta-hemolytic streptococci are Gram-positive cocci. Within actively spreading lesions, diplococcal forms predominate, whereas in purulent exudates, chain formation tends to occur.

The organisms have a capsule containing hyaluronic acid; the cell wall has three components:

(1) a protein component containing M, T, and R antigens;
(2) the carbohydrate moiety which contains rhamnose N-acetylglucosamine, the group-specific carbohydrate for the group A streptococci; and
(3) the peptidoglycan moiety.

The M protein is closely associated with the virulence of group A streptococci. It interferes with the ingestion of the streptococci by phagocytic cells.

In terms of pathogenicity, the group A beta-hemolytic streptococci must be deemed to possess the most impressive enzymatic and cellular armamentarium of any human pathogen. They produce a minimum of 20 extracellular products, including streptokinase (fibrinolysin) and streptodornase (deoxyribonuclease), hyaluronidase, diphosphopyridine nucleotidase, and hemolysins (streptolysin O and S).

The fibrinolysin and deoxyribonuclease function to liquefy viscous inflammatory exudates and in this way facilitate dissemination of the organism. The fibrinolysin is effective in the breakdown of the fibrin barrier which normally forms at the margins of inflammation, thus negating an additional host defense mechanism. Certain strains elaborate a diphosphopyridine nucleotidase which appears to possess the ability to kill leukocytes. Bacterial hyaluronidase can split hyaluronic acid, an important component of the ground substance of connective tissue, thus aiding in the spread of infection through connective tissue and fascial planes.

The streptolysin O is a protein which is hemolytically active in its reduced state. It is antigenic and forms the basis for the antistreptolysin titer; however, it is the streptolysin S (which is non-antigenic for man) that is responsible for the beta-hemolysis on the surface of blood agar plates.

FEMALE GENITAL TRACT INVOLVEMENT

The syndromes attributable to group A beta-hemolytic streptococci and whose occurrence and clinical manifestation directly involve the disciplines of obstetrics and gynecology are puerperal sepsis, prepubertal vulvovaginitis, endometritis-salpingitis, and necrotizing fasciitis.

Puerperal sepsis

While group A beta-hemolytic streptococci are unique in terms of potential pathogenicity, their mere presence within the bacterial flora of the female genital tract is not sufficient to produce disease. What is required is some breach of the mucosal barrier. Parturition is usually the event which provides the organism with an effective portal of infection. In rare instances trauma associated with coitus late in gestation may precipitate infection.

Antepartum infection due to the group A betahemolytic streptococci utilizes a different route of infection from that observed in the postpartum period. Infection spreads from the cervix or endocervix through the tissue planes of the uterus. Clinically, the patient presents with very high fever. Physical examination

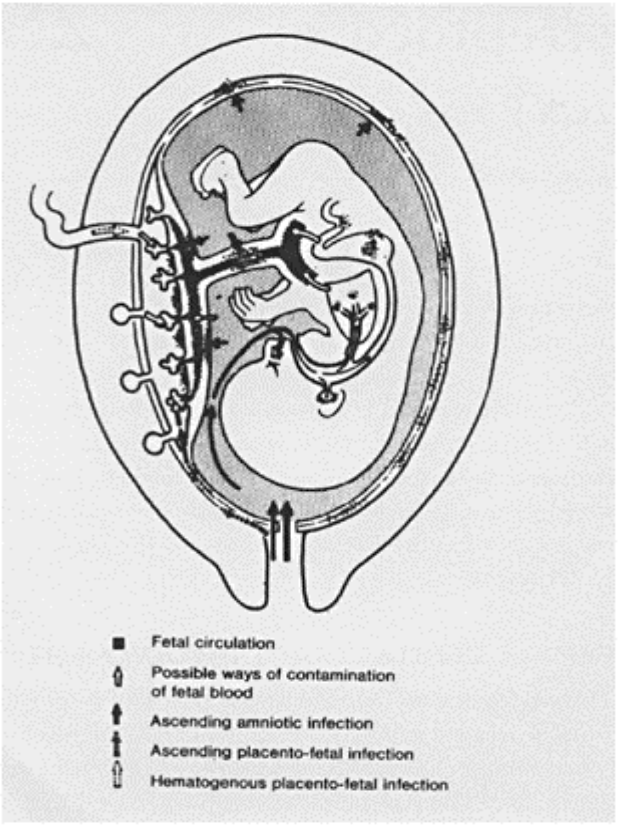

Figure 29.1 Routes of fetal infection (Blanc WAP. *J Pediatr* 1961; 59:473)

reveals nothing more than significant uterine tenderness. When the organism attains either the vascular implantation site or serosal surface, signs and symptoms of septicemia

ensue. At no time is there evidence of an exudative process at the endocervix. Maternal pyrexia and septicemia occur before fetal involvement (Figure 29.1). Even when the pregnancy is not at term, if the fetus is treated effectively with chemotherapy, an adverse fetal outcome may be totally averted.

In the pathogenesis of postpartum puerperal sepsis, two phases of disease can be discerned.

Phase of lymphangitic spread

Classically, the symptoms occur early—within 2–48 hours postpartum. Onset of the disease within the first 18 hours suggests that the group A beta-hemolytic streptococci resided within the patient's vaginal flora, whereas onset after 24 hours suggests possible acquisition of the organism from environmental sources.

Infection confined to the uterus and pelvis (parametrium) is clinically characterized by fever (38º-40ºC), leukocytosis (12000–20000 WBC/ml), tachycardia (110–120 heartbeats per min), and an edematous, soft uterus (uterine subinvolution). Exquisite pelvic tenderness involving both the adnexa and the cul-de-sac is usually demonstrable. The vaginal discharge tends to be serosanguinous and virtually free of odor. There is a pronounced diminution in the volume of lochia. Because of their invasiveness and virulence, the group A streptococci may produce fulminating infection with relatively unobtrusive localizing signs until peritonitis develops.

Peritonitis and systemic phases

With extension of the infection beyond the pelvis and the resultant peritonitis, patients develop the classic signs of puerperal sepsis, including shaking chills, flushed cheeks, glassy eyes, euphoria, distended tympanic abdomen, and absence of bowel sounds, in addition to those referable to infection limited to the pelvis. If the infection is not eradicated prior to this stage, bacteremia results, with possible secondary involvement of the lung parenchyma or heart valves and disseminated intravascular coagulopathy These complications may be manifested as a friction rub, evidence of pulmonary consolidation, the development of a cardiac murmur, and petechiae or oozing from surgical wounds, respectively. Death is usually imminent.

In the Sloane Hospital epidemic of 1927 reported by Watson and by Meleney *et al.* there were 25 cases of puerperal sepsis with 9 deaths. All but one of the patients who died in this epidemic exhibited positive blood cultures. Careful bacteriologic investigation clearly indicated that the vagina was the portal of entry. With the recognition of the natural history of the disease and the institution of rigid antiseptic and aseptic precautions, childbed fever due to group A streptococci should have been relegated to the history of medicine. Yet every now and then the organism circumvents precautionary measures and surveillance systems, and epidemic infection among puerperal patients occurs. In an epidemic in Boston, prompt and massive administration of penicillin in the early stages of the disease was responsible for limiting septicemia and thus the hazard of death. Even when septicemia occurred, no maternal mortality was observed.

Group A streptococcal infection of the female genital tract is often a hospital-acquired infection rather than an infection from an organism endogenous to the vaginal flora. The

recovery of this organism from a case of puerperal sepsis should alert the physician to the possibility not only of hospital acquisition but, even more important, to the potential for nosocomial spread. The individual responsible for bacteriologic surveillance in the institution should be notified immediately. If the infection is not an isolated occurrence, every attempt should be made to trace the pathway of bacterial dissemination and to institute rigid quarantine and isolation of known cases. The epidemiologic branch of the Centers for Disease Control may be of valuable assistance. In the Boston epidemic, penicillin was prophylactically administered to every new patient at admission and to the physicians intimately involved in therapy, in the hopes of eliminating organisms before they could either replicate to the point of clinical illness or become a source for additional dissemination.

Diagnosis

The clinical recognition of beta-hemolytic streptococci as markedly more virulent than their non-hemolytic counterparts prompted a classification based on the type of hemolysis and carbohydrate reaction. It was not until Lancefield demonstrated by precipitation tests that the streptococci contained group-specific carbohydrate substances (see Groups B, C, D and G streptococci) that the natural history of disease for the various subgroups was delineated. The hemolytic activity of the streptococci is the most misapplied feature of streptococcal classification and has engendered an inordinate amount of taxonomic confusion. Not all beta-hemolytic streptococci belong to the Lancefield group A. Betahemolysis does not necessarily imply pathogenicity; neither does an alpha- or gamma-hemolysis exclude it. The group A *S. pyogenes* are, in general, very susceptible to very low concentrations of bacitracin. The combination of these two characteristics, beta-hemolysis and bacitracin susceptibility, is presumptively diagnostic of *S. pyogenes*. Definitive identification is based on serologic testing for the group A polysaccharide antigen. This diagnosis has great potential consequences for the patient in view of the associated non-suppurative sequelae (rheumatic carditis and glomerulonephritis) which are observed exclusively with the group A organisms.

Therapy

The key to therapy is antibacterial chemotherapy in the form of potassium penicillin G administered IV. Erythromycin may be administered when patients demonstrate hypersensitivity to penicillin. Every effort should be made to ensure that there are no retained products of conception in the uterus. If any are identified, antibiotic coverage should be broadened to include *Bacteroides fragilis*, peptococcus, peptostreptococcus and *Prevotella*. The volume of the intravascular compartment should be restored. The patient should be isolated, and every attempt should be made to exclude an exogenous source of infection. Any hospital employee with a positive isolate from a nasopharyngeal, throat, skin, or rectal culture should receive 400000 units of phenoxymethyl penicillin (penicillin V) orally four times a day for 10 days. Once the culture is negative, the individual may return to work.

Antenatal streptococcal infection

Group A streptococcal infection in a pregnant patient with intact membranes may produce a distinct syndrome in the antenatal period. The prerequisite necessary to transform vaginal colonization into disease is presumed to be a breach of the mucosal-epithelial barrier. The portal of infection determines the ensuing symptom complex. When the labia minora or introitus is the site of initial infection, the patient presents with fever which is in excess of 39.5ºC and is extremely rapid in onset. Involvement of the external portion of the urethral meatus results in dysuria upon initiation of micturition. Physical examination reveals marked mucosal erythema and tenderness. When the cervix is traumatized by coitus late in gestation, the clinical presentation is virtually identical: sudden onset of significant fever. The pertinent physical findings are restricted to the uterus and peritoneum. Pelvic examination reveals diffuse uterine tenderness with or without parametrial tenderness. Rigors indicate involvement of the maternal implantation sites. The pathway of infection, with its ultimate involvement of the fetus, appears to be one of contiguous spread. Fetal infection occurs after maternal involvement. From the portal of infection, disease sequentially involves the endocervix, uterus, and products of conception. If maternal therapy is instituted early in the course of disease, the pregnancy is often unaffected.

Streptococcal vulvovaginitis

The group A, B, C, and G beta-hemolytic streptococci can produce an acute vulvovaginitis in prepubertal children and adults. Heller *et al.* have demonstrated group A streptococci *(S. pyogenes)* to be the etiologic agent in 10% of children seen at the Baltimore City Hospital with vulvovaginitis.

Vulvovaginal disease is due to direct mechanical transport of the bacteria from the nasopharynx to the vulvovaginal area. The same serotype of group A streptococci can be frequently demonstrated in both the vulvar and the pharyngeal sites.

Clinically, the patients present with vulvar pain, pruritus, and frequently dysuria (at the beginning of micturition). The vaginal discharge varies significantly in character so as to be non-diagnostic. The presence of diffuse vulvovaginal pain associated with a markedly erythematous mucosa should alert the clinician to the possibility of group A streptococcal vulvovaginitis. A presumptive diagnosis can be made from the Gram stain, but a definitive diagnosis is based upon bacterial confirmation. Because of the inability to differentiate group A streptococcal vulvovaginitis from that due to *Neisseria gonorrhoeae*, appropriate tests need to be employed which encompass these organisms.

Streptococcal disease readily responds to an oral penicillin or semisynthetic penicillin. Erythromycin can be effectively used in the penicillin-allergic patient.

Group A streptococcal endometritis salpingitis-peritonitis

Disease due to group A beta-hemolytic streptococci in the non-gravid female is not generally recognized. An acute endomyometritis may be triggered by the insertion of an intrauterine contraceptive device when group A beta-hemolytic streptococci are present

in the vaginal flora. Characteristically, patients have the onset of a high, spiking fever within 24 hours following insertion. Physical examination reveals the virtual absence of any inflammatory exudate. The only pertinent physical finding is exquisite uterine tenderness. If the infection is allowed to progress untreated, death may ensue.

The advent of culdocentesis coupled with anaerobic technology has radically altered our conception of what was once thought to be a well-defined entity, acute salpingitis. Monif *et al.* demonstrated that, *S. pyogenes* can be recovered as sole isolate from the cul-de-sac. The recovery of the organism and the ability to exclude the concomitant presence of class III obligatory anaerobes has focused on the probability that the group A streptococci under selective conditions can be a rare cause of acute salpingitis in the non-pregnant woman.

While a bacterium of unique virulence, the group A streptococcus requires a specific event such as a mechanical disruption of the cutaneous and mucosal barrier to initiate overt infection. The onset of menstruation appears to be an effective initiating event; consequently, the disease has a proximity to the onset of the menses which is not dissimilar from that characteristic of *N. gonorrhoeae*. The clinical manifestations are indistinguishable from those associated with *N. gonorrhoeae*. The incidence of acute salpingitis due to the group A streptococcus is low. Monif *et al.* identified a single case in a study of 92 patients with acute salpingitis. Eschenbach *et al.,* in their study of 241 cases of acute pelvic inflammatory disease, recovered *S. pyogenes* from the cul-de-sac in a single instance. In their case, as in that reported by Monif *et al.,* a pure culture of group A streptococci was recovered from the cul-de-sac.

Therapy involves IV penicillin G. Because of occasional non-susceptibility clindamycin and the tetracyclines are not deemed first-line drugs for group A streptococci.

Necrotizing fasciitis

As long ago as the Civil War, necrotizing fasciitis was recognized as a clinical entity. At that time it was known as *'hospital gangrene'*. The condition was first formally described in 1924 by Meleney, who applied the name *'hemolytic streptococcal gangrene'*. His description and therapy for this disease process are applicable today. The only significant alteration in therapy has been the introduction of antibiotics.

Clinical course

The portal of infection is established by a prior surgical procedure. The clinical course is rapid, with the patient exhibiting fever (38º-39ºC) and tachycardia which occasionally is out of proportion to the fever. With the onset of the disease, the patient usually experiences pain and swelling of the affected part. Chills and tremor are not uncommon. The initial pain is replaced by numbness which, in conjunction with the toxic metabolic state, usually renders the patient indifferent to her illness. On the second to fourth day of illness, the pathognomonic signs of streptococcal gangrene occur; to quote Meleney, 'these are dusky hue of the skin, edema with blisters, from which can be expressed a dark serosanguinous fluid. The margins are red, and swelling is neither raised nor clearly demarcated'.

On the fifth to eighth day, the discolored areas becomes frankly black or gray from gangrenous necrosis. Proportional to the severity of the disease, bacteremia is a common complication, with frequent metastatic involvement of the lung parenchyma. The disease process is one of extensive cellulitis complicated by abscess within fascial planes and widespread superficial fascial necrosis, resulting in separation and infarction of the overlying skin.

Streptococcal hyaluronidase is probably responsible for the destruction of connective tissue and the spread of infection along fascial planes. The fascia becomes liquefied and sloughs off. This disease entity is distinct from progressive synergistic bacterial gangrene, also described by Meleney, which is caused by microaerophilic streptococci in synergism with other organisms. It is interesting to note that Meleney's recorded mortality of 20–50% with the disease is the same as that indicated by present data. This high mortality and morbidity is partially the result of failure to recognize the pathognomonic features of this disease and institute early treatment. The late stage of the disease is difficult to check.

Diagnosis

Although a presumptive diagnosis can be inferred from the Gram stain, definitive diagnosis is contingent on bacteriologic identification. The organisms are found only in the subcutaneous slough. The surrounding edema is sterile. The causative agent is the group A *Streptococcus*. Secondary or associated organisms, such as *Staphylococcus aureus*, *Pseudomonas*, and diphtheroids, may be present, necessitating a distinction of this condition from progressive bacterial synergistic gangrene.

Therapy

The wound must be widely opened and the necrotic material removed. Long incisions to the ends of the necrotic areas are necessary to expose the involved tissue adequately. They are generally made in a stellate fashion out from the wound. The viable overlying skin may be left intact. The whole area is irrigated and packed open. Large doses of penicillin, administered intravenously, are also necessary. Because of the nature of the destructive process and the debridement, secondary closure is not possible and healing is by secondary intention. Grafting is sometimes necessary. Ventral hernias are frequent because of the loss of the abdominal wall fascia.

Streptococcal toxic shock syndrome

The group A streptococci causing a toxic shock-like syndrome belong to the M1 or M3 serotypes. They have been demonstrated to have the streptococcal pyogenes exotoxin A gene, a superantigen, and can stimulate T cells to proliferate non-specifically and cause the release of massive amounts of lymphokines and monokines. The exotoxin produces rapid skin and soft-tissue necrosis with fever, septic shock, and multiple organ failure. Bacteremia due to streptococci belonging to just the M1 serotype increased from 18% in 1979 to 64% in 1989–1990.

The group A beta-hemolytic streptococci can produce a clinical syndrome not too dissimilar from that due to the toxogenic strains of *S. aureus*. Disease usually occurs in a previously healthy individual and is characterized by marked systemic toxicity, rapidly progressive multi-system organ failure and a mortality of 30–60%.

Streptococcal pelvic infections are often associated with diffuse, non-localizing signs and symptoms. A prodroma of gastrointestinal symptoms such as vomiting and diarrhea and/or headache and myalgia may occur. Cervical exudate is usually sparse with little or no odor. Regardless of the site of primary infection, the patient presents with acute onset of very high fever and pain in the affected area; however, occasionally symptomatology referable to the primary site may not be conspicuous. Hypotension tends to develop in the first 24 hours. Mental status changes, oliguria, disseminated intravascular coagulopathy, biochemical evidence of hepatic dysfunction, and leukocytosis will manifest prior to respiratory and cardiovascular collapse, mortality exceeds 25%.

Streptococcal toxic shock has occurred with necrotizing fasciitis, endomyometritis, abortions and postpartum endocarditis. When streptococcal toxic shock syndrome ocurs in conjunction with necrotizing fasciitis, prompt and aggressive surgical removal of involved tissues is critical. Therapy entails aggressive use of beta-lactam antibiotics in conjunction with one or two doses (depending on renal status) of an aminoglycoside and, where indicated, surgical intervention in conjunction with use of a central venous line and intensive care support.

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30
Actinomyces israelii

Actinomyces israelii is an anaerobic, Gram-positive, branching filamentous bacterium whose filaments, by their radial attachment to the granule, give the organism its name: actino (radial), myces (mold-like). The diameter of the branching filaments is comparable to that of other bacteria; however, the overall length of the hyphae resembles that of molds measuring hundreds of thousands of microns.

The organism is a common saprophyte of the oropharynx and the intestinal tract. Under normal circumstances, it is incapable of penetrating intact anatomic barriers.

Actinomyces israelii is a strict anaerobe. Its pathogenesis in a given host is determined by this characteristic. Disease, when it occurs, is a function of a synergistic association between the anaerobic microbes of the *Actinomyces* group and other bacteria. Cultures of exudates confirm the observation that most, if not all, cases of actinomycosis represent mixed or combined infection. When material is analyzed at necropsy using special stains, organisms other than *Actinomyces* almost invariably can be demonstrated.

FEMALE GENITAL TRACT INVOLVEMENT

Actinomycosis is a progressive inflammatory disease with local or systemic manifestations, or both, characterized by a tendency to produce multiple draining sinuses. Infection of the female genital tract is an unusual variant of abdominal, disseminated, or ascending actinomycosis. The principal ways in which the female genital tract may be involved include:

(1) direct dissemination from a contiguous area;
(2) local lymphatic spread from contiguous areas (e.g. a ruptured appendix or inflamed colonic diverticula);
(3) hematogenous dissemination during systemic infection; and
(4) possible ascending infection associated with a contraceptive intrauterine device (IUD) (Figure 30.1).

The interim between initial systemic seeding of the female genital tract and onset of disease may be prolonged. A case of tubo-ovarian involvement occurred 6 years and 11 months after a ruptured appendix. When involvement of the genital tract is secondary to widespread systemic disease, initial infection appears to occur within the distal portion of the fallopian tubes. In this respect, actinomycosis behaves very similarly to tuberculosis. Endometrial and ovarian involvement are usually secondary to tubal disease.

The initial pathologic process is abscess formation. Physical expansion of an encapsulated organ or inflammatory neuritis may make pain a prominent symptom. The abscesses tend to burrow, eventually resulting in tortuous sinus tracts composed of dense

fibrous connective and granulation tissue surrounded at the margins by a chronic inflammatory infiltrate. Within the lesions aggregate colonies of the organism, known as ‘sulfur granules’ can be demonstrated (Figure 30.2). Infection is contingent on synergistic, facultative, anaerobic bacteria creating a low oxidation-reduction potential; consequently, contagion is not a major consideration.

A small percentage of women, by choosing the IUD as their mode of contraception, appear to develop a chronic polymicrobial infection of the endometrial cavity which ultimately becomes clinically manifested. Endometrial involvement appears to be due to an ascending infection. Burnhill has described a syndrome of progressive endometritis characterized by foulsmelling intermenstrual leukorrhea, metrorrhagia, premenstrual bloating, and menorrhagia. Papanicolaou smears from such patients have often demonstrated

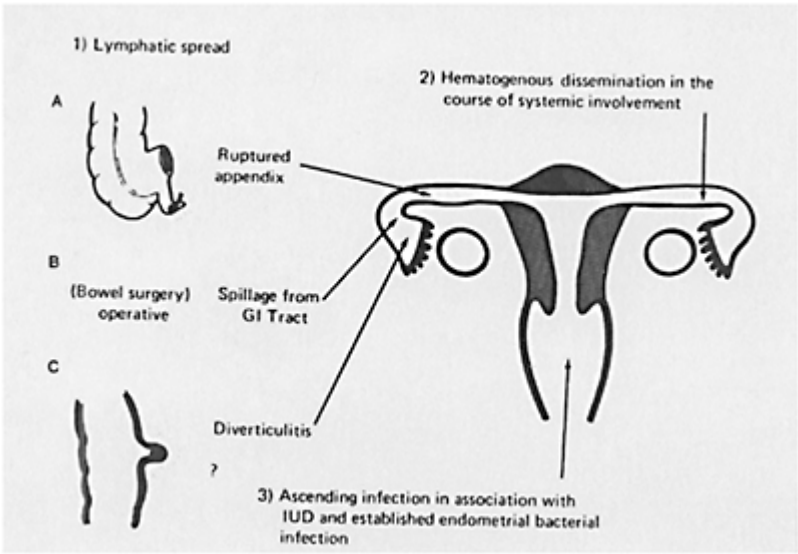

Figure 30.1 Mechanisms of involvement of the female gential tract by *Actinomyces israelii*. GI, Gastrointestinal; IUD, intrauterine device

collections of pseudomycelial bacteria which by immunofluorescence can be demonstrated to be *A. israelii*.

A significant number of these patients have developed a unilateral abscess associated with IUD utilization or shortly after its removal. It is postulated that the development of a unilateral tubo-ovarian abscess is an expanded manifestation of anaerobic endometritis. The presence of *A. israelii* in the polymicrobial bacterial infection may be one of the factors predisposing to this complication.

DIAGNOSIS

Although used for taxonomic identification, serologic tests are devoid of diagnostic value. Both immediate and delayed types of skin reactions have been observed in actinomycotic patients; however, the nonavailability of antigenic material for cutaneous challenge limits the clinical usefulness of this procedure.

Diagnosis of actinomycosis is often inferred from a fresh smear or a simple Gram stain smear of exudate or aspirated material. A fresh smear of pus or exudate may reveal a tangled mass of wavy organismal threads, the so-called yellow ‘sulfur granules’. These characteristic mycelia-like collections are often scanty. Their identification often depends on extensive searching of smears of histologic sections or necrotic material. Sulfur granules *per se* are not pathognomonic of actinomycosis. Both *A. israelii* and *Nocardia asteroides* may produce them. The two organisms can be distinguished on the basis of histochemical staining. Whereas *N. asteroides* is acid-fast, *A. israelii* is not (unless the Putt modification of the Ziehl-Neelsen acid-fast method is used). The sulfur granules of *A. israelii* are sometimes confused with clusters or colonies of other bacteria growing in an anaerobic environment. The greater affinity of *A. israelii* for silver stains provides one means of histologic differentiation between the two conditions.

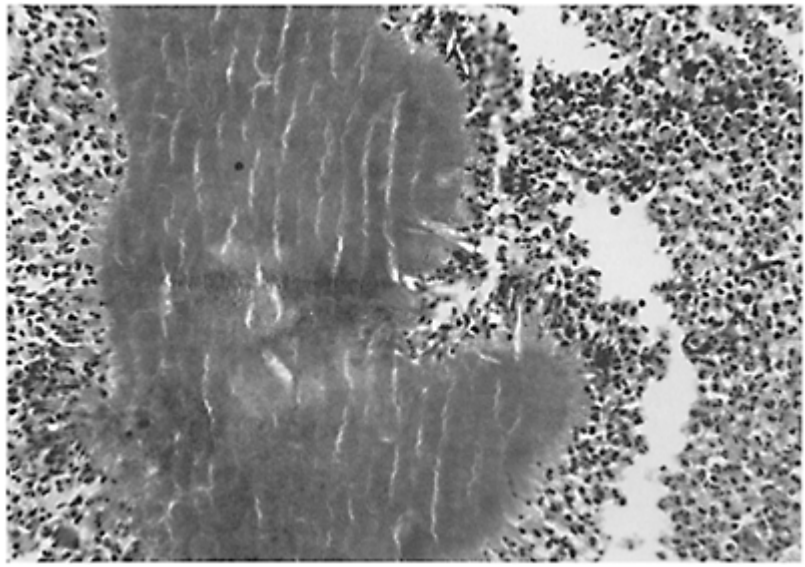

Figure 30.2 Sulfur granules of *Actinomyces israelii* showing the radial arrangement of branching filamentous organisms which stain positive with Gram and silver stains, surrounded by necrotic debris and acute inflammatory cells. (H&E, ×140)

Actinomyces israelii can be grown if appropriate anaerobic culture techniques and media are used. Culturing of the organism provides the definitive means of identifying it as the causative agent.

THERAPY

Actinomyces species are sensitive to penicillin, ampicillin, the tetracyclines, chloramphenicol, clindamycin, and selected aminoglycosides. In dealing with deep-seated, soft-tissue infections of the female genital tract, chemotherapy is more than an adjunct to surgical resection of diseased tissue; it is a necessary prerequisite. Prior to an operative procedure, it is recommended that a patient receive penicillin, an erythromycin or doxycycline. The extent of the disease determines the drug dosage and its duration of administration.

When fallopian tube involvement is secondary to spillage from the GI tract, gastrointestinal maximum shrinkage of an abscess with antibiotics should be attempted. If the disease is still evident after adequate therapy, or if a single relapse occurs, surgical removal of diseased tissue under antibiotic coverage is indicated.

Therapy for localized disease associated with IUDs requires a degree of individualization. If the patient with pseudomycelial clumps of bacteria is asymptomatic and the pelvic examination does not reveal cervical tenderness to motion or an adnexal mass, very often mere removal of the IUD is sufficient to eradicate disease. If the IUD presents with either menstrual irregularities or Burnhill's syndrome, it has been the author's policy to place these patients on antibiotics prior to the removal of the IUD. If the pelvic examination is abnormal, aggressive antibiotic therapy should be implemented to eradicate the symbiotic polymicrobial infection which frequently includes members of the *Bacteroides* or *Prevotella* species. If an adnexal mass does not respond to antibiotic therapy and surgery is required, as conservative an operation as technically possible should be carried out.

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31
Bacteroidaceae

The family *Bacteroidaceae* consists of Gram-negative non-spore-forming anaerobic bacilli which constitute one of the major groups of anaerobes that function effectively as class III anaerobes (obligate anaerobes). These bacteria can be differentiated from other organisms of this schema by morphology, biochemical characteristics, and identification of metabolic end products by gas liquid chromatography (GLC). The bacteroides, *Prevotella* and the fusobacteria are the most commonly found organisms of this group. Morphologically, *Bacteroides* and *Prevotella* appear as rods with rounded ends or as coccobacilli. Fusobacteria are generally characterized by long, thin fusiform shapes or extremely pleomorphic spherical forms.

Therapeutically, the *Bacteroides/Prevotella* species can be subdivided for pragmatic purposes into the penicillin-sensitive and the non-pencillin-sensitive bacteroides. The ability to function as an effective pathogen for the female genital tract is independent of the bacterium's relative sensitivity to penicillin. Originally, the *Bacteroides* were subdivided into bile-resistant and bile-sensitive organisms. The principal bile-resistant species were *B. fragilis, B. distasonis, B. vulgatus, B. ovatus, B. thetaiotaomicron* and *B. uniformus*. The major bile-sensitive species included *B. bivius, B. disiens, B. capillosus, B. gracilis, B. ureolyticus, B. oralis, B. melaninogenicus* and *B. asaccharolyticus*.

In recent years, the taxonomy of anaerobic Gram-negative bacilli has been in a state of great change, and this trend will continue. The genus *Bacteroides* has been restricted to the *Bacteroides fragilis* group only (including *Bacteroides eggerthii*); the taxonomic positions of other species still included in the genus *Bacteroides* remain uncertain, but all of these species will ultimately be transferred to other genera. As currently constituted, the *B. fragilis* group includes: *B. caccae, B. distasonis, B. eggerthii, B. fragilis, B. merdae, B. ovatus, B. stercoris, B. thetaiotaomicron, B. uniformis, B. vulgatus.*

This bile-resistant *B. fragilis* group is the most commonly recovered anaerobe in clinical specimens and is more resistant to antimicrobial agents than are most other anaerobes. *B. fragilis* and *B. thetaiotaomicron* are of the greatest clinical significance.

The genera *Prevotella* (saccharolytic) and *Porphyromonas* (pigmented asaccharolytic organisms) were previously included in the genus *Bacteroides*. *Prevotella* species are the bile-sensitive, non-pigemented, saccharolytic Gram-negative bacilli. *Prevotella* species are found in the same settings as the pigemented Gram-negative rods. *Prevotella bivia* and *Prevotella disiens* are found in female patients with genital tract infections.

Porphyromonas (Bacteroides) melaninogenicus is a monomorphic (i.e. not pleomorphic) species, characterized by the formation of a black pigment on blood agar. *P. melaninogenicus* is part of the normal flora of mucous membranes and is commonly found in anaerobic infections originating from the genital tract. It is frequently found in assocation with peptostreptococci. The two organisms may act synergistically.

Bacteroidaceae are relatively common anaerobic female genital tract isolates. The bacteria has been cultured in the cervix, placenta, and/or amniotic fluid of gravida with premature or prolonged rupture of the fetal membranes.

Anaerobic bacteria may colonize amniotic fluid in the absence of ruptured membranes. The frequency with which anaerobic bacteria enter into amniotic fluid is significant, yet progression to disease, chorioamnionitis, or perinatal septicemia is not a common phenomenon. A potential explanation for this discrepancy between infection and disease rates may be inferred from the prerequisites for disease. Amniotic fluid preferentially supports the growth of class I (bacteria that replicate better in the presence of air than in its absence) over class II (microaerophilic) anaerobic bacteria. For the *Bacteroidaceae* to function effectively, some change must occur in its local microbiologic environment. Meconium enhances anaerobic replication by lowering the oxidation-reduction potential.

PATHOGENESIS

The *Bacteroides* and *Prevotella* species exist as microaerophilic constituents of the female genital tract, being present usually as class II anaerobes, which are defined as bacteria that are unable to initiate growth unless the oxidation-reduction potential of the medium is low or unless they are present in an extremely large number. The transformation from a state of colonization to a state of disease can be achieved by two major pathways:

(1) the anaerobic progression; and
(2) the immediate anaerobic syndrome.

The mandatory prerequisite in each case is an alteration of the oxidation-reduction potential.

THE ANAEROBIC PROGRESSION

The anaerobic progression has its genesis with bacteria whose ability to replicate at different oxygen levels varies significantly. The polymicrobial infection present at the initiation of anaerobic disease undergoes selective changes as the consequence of the induced alterations in the microbiologic environment. As the oxidation-reduction potential is lowered, acidification of the local environment occurs and molecular oxygen is removed; the more aerobic bacteria, which are unable to replicate under these adverse conditions, undergo the process of autoelimination. Sequential samplings of what is ultimately to be an abscess due to *B. fragilis* might reveal *B. fragilis* present as a class II anaerobe with such bacteria as *Escherichia coli*, *Staphylococcus epidermidis*, the enterococci (group D streptococci), *Gardnerella vaginalis*, and the peptostreptococci. When the environmental requirements for anaerobic dominance are achieved and the anaerobic progression has shifted from organisms of class II to class III, many of these cofacilitating bacteria undergo auto-elimination so that *Bacteroides* and peptostreptococci, either singly or in combination, predominate.

The ultimate result of anaerobic infection is abscess formation. In a well-established abscess, one rarely finds more than one or two types of bacteria. In an evolving abscess, a more polymicrobial representation of bacteria is to be anticipated. Factors which predispose to anaerobic infection include:

(1) new tissue space, e.g. hematoma;
(2) necrotic tissue as might be present with incomplete abortions or retained products of conception, criminal abortions, degenerated tumor masses, crush injury, or devitalization of previously healthy tissue;
(3) penetration of the gastrointestinal tract with spillage of fecal material; or
(4) alteration of the microbiologic environment by *Neisseria gonorrhoeae*.

Under these conditions the probability of the *Bacteroidaceae* functioning as effective pathogens in the female genital tract is great.

Many of the *Bacteroides* strains elaborate betalactamases which can protect beta-lactamase-sensitive constituents, e.g. enterococci, until a critical oxidation-reduction potential is reached which allows the *Bacteroides* strain to function as a monomicrobial pathogen.

All members of the *B. fragilis* group appear to be able to encapsulate during an inflammatory process. Nonencapsulated strains can become encapsulated with the assistance of their aerobic counterparts in the anaerobic progression. These encapsulated strains are more virulent to the host than non-encapsulated strains. This increased virulence can be demonstrated by a higher rate of induction of bacteremia, and a greater enhancement of growth of other bacteria. Antimicrobial therapy directed only at the eradication of aerobic bacteria does not prevent encapsulation or reduce the number of *Bacteroides* species.

IMMEDIATE ANAEROBIC SYNDROME

The right microbiologic environment can be combined with the right bacteria to produce disease. This sequencing of events is called the immediate anaerobic syndrome, the classical example of which is either spontaneous or iatrogenic perforation of the gastrointestinal tract. The oxidation-reduction potential of feces is one of the lowest recorded. The bacterial flora of the gastrointestinal tract is predominantly anaerobic. The spillage of fecal material requires no intermediary events for the production of anaerobic infection.

CLINICAL CONSEQUENCES

Endomyometritis-septic thrombophlebitis-septicemia

Under normal physiologic conditions the endometrial cavity has no demonstrable bacterial flora. Even when organisms are iatrogenically introduced, as with insertion of an intrauterine contraceptive device, bacterial replication (barring the presence of group A beta-hemolytic streptococci) is not sustained. Within a relatively short time after

insertion of the device, transcervical cultures of the endometrial cavity are again sterile. In the postpartum period, the endometrium represents a functional tissue system whose normal defense mechanisms have undergone significant alteration. The loss of mucosal integrity and the presence of blood and a necrotic decidua sustain bacterial colonization. Transcervical aspiration almost invariably documents the occurrence of bacterial replication. When one is dealing with nonquantitative data, the major bacteriologic difference between infected and non-infected endometria (excluding infection due to *N. gonorrhoeae,* group A betahemolytic streptococci, and *Listeria monocytogenes*) is a shift toward the more obligate anaerobes.

What is impressive is the ability of the endometrial cavity to limit the number of instances in which bacterial replication progresses to infectious morbidity. Unless there are retained products of conception, or the mode of delivery has been a cesarean section, the presence of other synergistic or facilitating organisms is not sufficient to sustain anaerobic dominance by the *Bacteroides/Prevotella*. In these instances, *Bacteroides/Prevotella* may participate as part of a mixed aerobic/anaerobic low-grade endometritis that is usually not clinically discernible.

The situation is markedly altered when one is dealing with retained products of conception or with an infected uterus after cesarean section. In the former and as a consequence of the altered oxidation-reduction potential engendered, the *Bacteroides* or *Prevotella* alone or in conjunction with the anaerobic streptococci and/or the anaerobic staphylococci produce disease. Patients present with fever, a foul-smelling lochia, and uterine tenderness. If the process is not arrested by surgical removal of the retained products of conception, it may progress to involve the maternal implantation site, in which case septic thrombophlebitis and septicemia may develop. *Bacteroides* can spread in the clots within the thrombosed sinuses to the uterine and ovarian veins. More extensive spread involves the iliac veins, the inferior vena cava, and the renal vein. The patient develops chills and hectic fevers, which are often accompanied by rigors. Subsequent pleuritic chest pain and hemoptysis may indicate pulmonary emboli and segmental infarction of the pulmonary parenchyma. Careful inspection of the placenta is one of the most effective means of averting this sequence of events.

Puerperal infection from septic abortion

In terms of fulfilling the major prerequisite for *Bacteroides/Prevotella* infection, namely, a low oxidation-reduction potential, septic abortion, whether spontaneous or induced by instrumentation, creates a condition analogous to that observed with retained products of conception. In the absence of more virulent pathogens within the vaginal flora, *E. coli,* group B betahemolytic streptococci, and enterococci are often the leading organisms. However, they may be subsequently superseded by the more obligate anaerobes. The amount of tissue available for bacterial replication and the direct access to the maternal vascular compartment or the presence of peritonitis secondary to uterine perforation sets the stage for sustained septicemia, which in turn can be correlated with maternal morbidity and possibly mortality. The situation here is analogous to a patient’s being administered a continuous intravenous infusion of bacteria. The key to therapy in this situation consists of surgically disconnecting the intravenous line while aborting potential metastatic complications with antibiotics.

Perinatal septicemia

A subgroup of neonatal septicemia has been established, based on perceived differences in the events that combine to produce disease. Septicemia in the first 24–48 hours of life is termed perinatal septicemia, whereas that occurring after 48 hours is termed neonatal septicemia. Maternal factors such as chorioamnionitis, urinary tract infection, and prolonged and/or premature rupture of the fetal membranes predispose to perinatal septicemia. In contrast, neonatal septicemia occurring after the first 48 hours is primarily a nosocomial disease of infants who are debilitated or chronically ill (e.g. those with congenital anomalies, necrotizing enterocolitis) or who have been anatomically compromised (e.g. by surgical procedures or central line complications).

There are very few demographic factors that distinguish anaerobic perinatal septicemia (specifically that due to *Bacteroidaceae*) from its aerobic counterpart. Maternal chorioamnionitis, fetal distress, and perinatal respiratory difficulty are common to both. A foul-smelling neonate is evidence of anaerobic replication *in utero*. In the series of Chow *et al.*, eight of nine newborns with a foul smell at birth had *Bacteroides*. Both cases of *Bacteroides* perinatal septicemia reported by Keffer and Monif occurred in women who had intact fetal membranes until the immediate parturition period.

Foul-smelling amniotic fluid and/or a maternal history of prolonger labor with intact membranes, coupled with a potentially septic neonate, should alert the neonatologist to the possibility of anaerobic infection from a member of the *Bacteroidaceae/ Prevotella*. Many of the *Bacteroidaceae/Prevotella* are resistant to a penicillin-aminoglycoside combination. In terms of perinatal outcome, failure to adequately cover for the penicillin-resistant isolates may be equivalent to delayed therapy.

DIAGNOSIS

The diagnosis of *Bacteroides* infection must emanate from the physician and not the clinical laboratory. By having insight into the pathogenesis of the anaerobic infections, one can often anticipate those clinical situations in which *Bacteroides* may represent a significant portion of the group of bacteria that have combined to produce disease. Certain clinical situations carry with them a high probability of organismic participation:

(1) postpartum endometritis associated with retained products of conception;
(2) postpartum endomyometritis in patients who have undergone cesarean section;
(3) septic abortion;
(4) septic thrombophlebitis; and
(5) any abscess (irrespective of site), particularly one that had access to the vaginal flora or is the consequence of penetration of the gastrointestinal tract and spillage of fecal material.

A prospective orientation to the problem is best. However, the diagnosis of *Bacteroides/Prevotella* infection is sometimes suggested by the failure of infectious morbidity to respond to beta-lactam antibiotics.

The mortality rate due to perinatal septicemia is directly contingent on the interim between onset of disease and initiation of effective antibiotic therapy. Monif *et al.* demonstrated that when therapy was delayed for more than four hours, 80% of the infants

died or had residual sequelae. The possibility of a penicillin-resistant strain should influence antibiotic selection.

If anaerobic collection containers are not available, Gram-staining becomes the most important diagnostic tool next to the physician's ability to anticipate participation by *Bacteroidaceae*. As previously stated, the presence in smears from body fluids or abscesses of Gram-negative pleomorphic rods that fail to grow in aerobic cultures should suggest the *Bacteroidaceae/Prevotella*.

THERAPY

Antibiotic selection significantly depends on whether the process is in evolution or whether the critical conditions for anaerobic dominance have been met. The contention of Gorbach and Bartlett (personal communication) that by treating the synergistic component one can

Table 31.1 Advocated antibiotic regimens in the treatment of infections due to the penicillin-resistant *Bacteroidaceae/Prevotella*

Degree of efficacy	***Drug***		***In vitro susceptibility***
Penicillin-resistant *Bacteroidaceae/Prevotella*	Chloramphenicol*		98%
	M etronidazole*†		94–96%
	Clindamycin*		70–85%
	Doxycycline‡		80–85%
	Cefoxitin		72–85%
	Ureidopenicillins		60–70%
Category designation		Ampicillin/sulbactam**	
		Chloramphenicol*	
		Clindamycin*	
		Imipenem	
		Metronidazole*	
Antibiotics with reasonable effectiveness		Cefoxitin	
		Doxycycline	
		Trovofloxacin***	
		Ureidopenicillin	

*Chloramphenicol, clindamycin, and metronidazole each carry an FDA black box indicating possible dangerous or lethal adverse drug reaction.
†The intravenous form of metronidazole has been released for the treatment of anaerobic infections; consequently, the correlation between *in vitro* and *in vivo*, while probably excellent, is not as well substantiated as for chloramphenicol and clindamycin.
‡Must use 300 mg/day to achieve these percentages, which exceeds FDA recommendations but is commonly used.
**Other 'fifth generation' penicillin may also have category designation.
***Excellent *in vitro* data may well correlate with clinical data

disrupt the anaerobic progression appears to be valid so long as it is restricted to the early phase of disease. Once obligate anaerobic dominance has been established, all the bacterial constituents in the synergism should be treated with appropriate antibiotics to effect a definitive cure (Table 31.1).

The *Bacteroides/Prevotella* pose a difficult problem to clinicians because of their ability to produce the enzyme beta-lactamase. Resistance of most anaerobic Gram-negative bacteria to beta-lactam antimicrobial agents is primarily mediated by the production beta-lactamases. A great variation in specific activity has been demonstrated among enzymes from different *Bacteroides/Prevotella* strains. Consequently, coverage in both categories I and II of the Gainesville Classification needs to be implemented. The drugs of choice are clindamycin, imipenem, and metronidazole. There have been two major attempts to overcome resistance to beta-lactam drugs:

(1) Coupling of semisynthetic penicillins with beta-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam. The inhibitors produce a marked reduction in MIC^{50}s and MIC^{90}s for the companion penicillin, and
(2) the development of antibiotics which are more resistant to degradation by beta-lactamase enzymes. Some modifications including the 7 alpha-methoxy cephalosporins (cefoxitin, cefotetan, moxalactam) and the 7 beta-methoxy aminoacetamide cephalosporins (cefotaxime and cefmenoxime) have greatly enhanced efficiacy against the Bacteroidaceae.

In contrast to the *Bacteroides/Prevotella*, the *Fusobacterium* do not produce beta-lactamase and consequently are sensitive to the penicillins.

Because of the increasing resistance to clindamycin and metronidazole and the rapid induction of resistance to imipenem, selective use of ampicillin-sulbactam and ticarcillin-clavulanic acid and possibly piperacillin-tazobactam appears warranted.

Although metronidazole can be readily substituted for clindamycin in the context of triple therapy for category II coverage in the Gainesville Classification, its failure to cover the aerobic Gram-positive bacteria of category I precludes its combination with just an aminoglycoside. Effective preliminary antibiotic coverage requires the concomitant administration of an antibiotic whose spectrum of susceptibility encompasses both Gram-positive and Gram-negative aerobic bacteria.

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32
Clostridium perfringens

Clostridium perfringens is a Gram-positive, anaerobic, non-motile, spore-forming rod which is often encapsulated and capable of producing potent exotoxins. The bacterium is subdivided into five types based upon the production of four major lethal toxins: alpha, beta, epsilon, and iota. The most important toxin is alpha toxin, a lecithinase that destroys cell membranes, alters capillary permeability, destroys platelets, and causes severe hemolysis. In appropriate environmental conditions, vegetative forms of the histotoxic clostridia replicate and elaborate toxins that diffuse into adjacent soft tissue and promote local spread as well as extensive systemic effects. Despite its relatively high prevalence in the lower gastrointestinal tract bacterial flora, *C. perfringens* is a rare isolate from the female genital tract.

Two explanations have been advanced to explain the disassociation between bacterial isolation/infection and disease. The first is that of variability in the toxigenicity of individual strains of *C. perfringens*. The alternate hypothesis has to do with variability in the conditions necessary to produce disease. Holtz and Mauch postulated that primarily three conditions are necessary for the development of clostridium myonecroses, which are:

(1) the organism must be introduced into the uterus from an outside source or must be carried into the uterus from the vagina or cervix;
(2) dead tissue must be present at the time the organisms are introduced; and
(3) the injured tissue must remain in the uterus for sufficient time to permit incubation of the organisms.

One can readily visualize situations in which, despite vascular access, conditions necessary for toxic production might be transient; e.g. transient retention of a larger fragment of necrotic decidua. Neither theory is mutually exclusive.

The time over which *C. perfringens* can produce toxins influences both morbidity and lethality. In obstetric and gynecological patients, the severity of extrauterine manifestations of disease is a partial function of the extent of pelvic tissue necroses. Within necrotic tissue, the production of exotoxins requires approximately 24–28 hours of incubation. The exotoxins necrotize surrounding normal tissue, especially muscle, thereby creating a wide area for invasion by the proliferating organisms.

The exotoxins produce the full-blown syndrome of *C. perfringens* septicemia, characterized by hemolysis, hemoglobinemia, hemoglobinuria, hyperbilirubinemia, acute renal failure, hyperkalemia, and diffuse intravascular coagulation (DIC). The alpha toxin, a lecithinase, causes lysis of the red blood cell membrane. Hemoglobin is liberated and circulates as free hemoglobin in the plasma, producing the characteristic portwine colored serum and urine. Acute renal failure is due to acute tubular necroses secondary to renal ischemia. Hyperkalemia is a result of the liberation of potassium from hemolyzed red

blood cells compounded by an inability to excrete this overload in the presence of renal failure. DIC is due both to the action of alpha toxin on the vascular endothelium and release of a thromboplastin-like substance.

CLINICAL MANIFESTATIONS

Clostridial myonecrosis

The usual clinical setting for cases of clostridial myonecrosis (gas gangrene) due to *C. perfringens* is that of criminal abortion, retained products of conception or endomyometritis. Nevertheless, a wide clinical spectrum is observed with clostridial septicemia, ranging from a relatively benign course to septic toxemia with renal failure due to massive intravascular hemolysis and death. Markedly less frequent is the occurrence of clostridial myonecrosis following a surgical procedure. The determining factor governing the severity of disease is the local oxidation-reduction potential. A sustained decreased oxidation-reduction potential promotes toxin production. With the exception of septic abortion, overwhelming sepsis is a relatively rare event. However, when serial blood cultures are done in cases of endomyometritis following cesarean section, an occasional case can be identified in which *C. perfringens* is isolated from the intravascular compartment; the clinical course is one that readily responses to antibiotic therapy.

With postabortion and puerperal uterine infections, *C. perfringens* can produce a low-grade endometritis. Patients present with vaginal discharge, uterine tenderness and fever. There are no signs of systemic toxemia. The diagnosis is suggestive by the identification of large Gram-positive rods on Gram-staining and confirmed by the growth of *C. perfringens* in culture specimens. Ramsey noted that in his series of 190 cases of postabortion sepsis in which clostridia were isolated from the cervix, 130 (66%) were mild infections localized to the uterus, and response was rapid. In the 15% of postabortion clostridial infections with clostridial bacteremia, two-thirds had no clinical evidence of systemic infection.

The key for the induction of postabortal clostridial disease is the presence of necrotic tissue which occurs with incomplete abortion or an intrauterine fetal demise. In these cases, clinical response to dilation and curettage, coupled with effective antibiotic therapy, is rapid. When the underlying causation is due to excessive tissue destruction, as would occur with abortions induced by caustic agents or injection of hypertonic saline into the myometrium during intra-amniotic infusion, or significant delay in therapy occurs, the patients develop severe endomyometritis, peritonitis and septicemia.

Clinically, the patients usually present with fever and abdominal pain. On physical examination, an elevated temperature, uterine tenderness and the presence of a foul-smelling discharge are usually demonstrable. The diagnosis may be inferred by the identification of large Gram-positive, box-like rods on Gram-stained smears. With progression of clostridial disease, the consequence of alpha toxin production is manifest. Full-blown clostridia septic toxemia is characterized by intravascular hemolysis, hemoglobinemia, hemoglobinuria, hypotension and renal failure. Depending upon the quality and timing of interventions, the ensuing mortality ranges from 21–85%.

Soft tissue clostridial infections

Soft tissue clostridial infection in the gynecological patients requires, in addition to bacterial access to the site of infection and tissue necrosis, poor tissue perfusion. In the non-pregnant woman, clostridial myonecrosis tends to occur primarily in irradiated or diabetic patients or in patient with either benign (leiomyoma) or malignant genital tract tumors which have undergone significant necrosis. When clostridial myonecrosis complicates these types of cases, a higher than expected mortality rate occurs, owing primarily to the failure of recognizing clostridia superinfection after surgery. Postoperatively, the development of severe pain and systemic toxicity, which is out of proportion to the physical finding, should alert the clinician to the possibility of clostridial infection.

In the absence of extensive trauma to the operative site, surgical wound infections rarely develop clostridia myonecrosis. Clostridia may be isolated from a simple wound infection. However, unless there is an extensive area of tissue necrosis or hematoma formation, the process is limited, and the impact of alpha toxin production is relatively negligible.

DIAGNOSIS

The diagnosis is usually made in one of three ways:

(1) recovery of *Clostridium perfringens* from a wound or blood culture;
(2) visual or roentgenographic evidence of myocerosis with gas fermentation (Figure 32.1); or
(3) a clinical picture suggestive of toxigenic clostridial sepsis.

Pain, which is caused by the rapid infiltration of muscle by edema and gas, is the earliest symptom. When pain is the result of trauma, disease appears within 24–72 hours of the event. A tachycardia out of

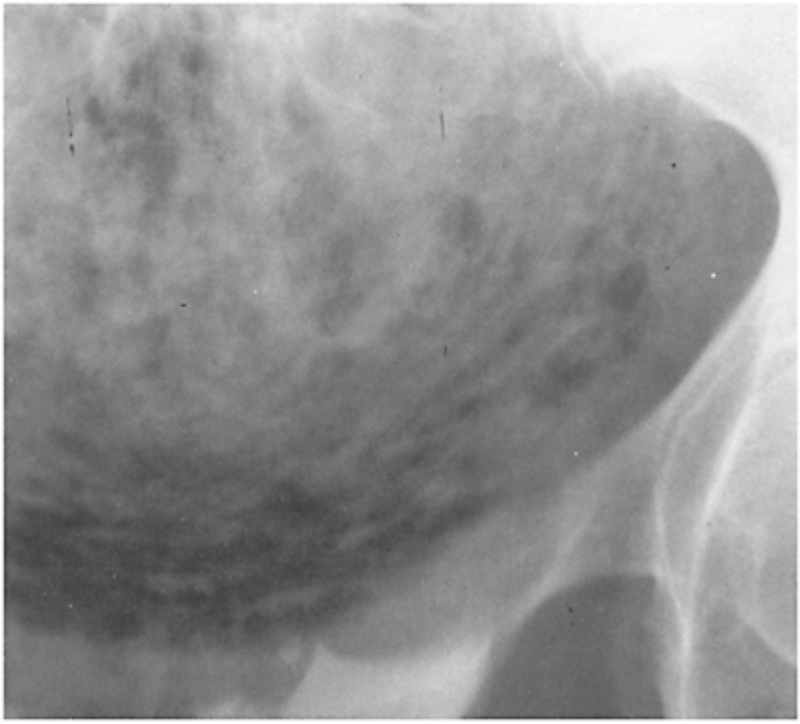

Figure 32.1 Gas formation in the pelvic tissues of a woman with postpartum endomyometritis due to *Clostridium perfringens*

proportion to the temperature is characteristic. A subnormal temperature with a marked tachycardia is a grave prognostic sign.

When the site of myonecrosis is visible, the appearance of the wound is that of an edematous, purulent wound with brownish, bubbling exudate. Crepitation may be demonstrable in the adjacent tissues. The surrounding skin becomes edematous and has a brown discoloration termed ‘brown erysipelas’. Gram-stained smears reveal the presence of large Gram-positive rods.

The full-blown syndrome of clostridial sepsis include hypotension, intravascular hemolyses, hemoglobinemi, hemoglobinuria, jaundice and renal failure. The skin exhibits a gray pallor, and profuse diaphoreses may be present. The patient may be apathetic and indifferent to her condition. X-ray films can usually demonstrate spread of the gas in the involved tissues. A definite diagnosis is based on bacteriological identification of *C. perfringens*.

THERAPY

Most cases of postabortal or postpartum endometritis/ endomyometritis without evidence of intravascular hemolysis do well with removal of necrotic tissue and appropriate antibiotic therapy. The isolation of clostridium from the uterus or bloodstream is not indicative, by itself, of a severe infection. The development of intravascular hemolysis in association with clostridial infection is a poor prognostic sign and delineates a group of patients with potentially lethal infections. Once clostridial organisms are identified on a Gram-stained smear from the site of infection in a septic patient, prompt surgical intervention is urged.

Better than 80% survival rates can be achieved with early aggressive therapy that includes antibiotics, prompt operative debridement of necrotic tissue with removal of the nidus of infection, which is the source of the exotoxins responsible for the clinical findings, and prompt medical therapy of acute renal failure. In severe uterine and pelvic infections, total abdominal hysterectomy and bilateral salpingoophorectomy may be required.

The most important component of therapy is prompt and extensive surgical removal of infected tissue when disease involves the uterus. Hysterectomy is indicated. With wound infection and myonecrosis, extensive surgical debridement with wide excision of involved muscle when the abdominal wall is involved need to be carried out. When available, antecedent hyperbaric oxygen therapy facilitates surgery by increasing the visual demarcation between visible and dead tissue.

Early antimicrobial therapy is essential for optimal outcome. Penicillin G in dosages of 10–24 million units per day is advocated for severe infection. Alternative therapy includes metronidazole and clindamycin. Cefoxitin is less active against clostridia than most other cephalosporins and should be avoided. Antitoxin therapy is no longer available commercially. The high frequency of allergic reactions and a relative lack of efficacy were the reason behind discontinuations.

The timing of hyperbaric oxygen continues to be controversial. If laparotomy or hysterectomy is indicated, the operation should not be delayed for hyperbaric oxygen therapy. Hyperbaric oxygen before surgery has the benefit of clearly demarcating involved tissue, thus potentially sparing viable tissue while halting toxin production. If used, hyperbaric oxygen should be available within a 1-hour time frame.

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33
Clostridium sordellii

Clostridium sordellii was considered merely as a common soil and enteric bacterium that was infrequently recovered from the vagina.

C. sordellii has been shown to cause puerperal infection and a distinctive and lethal toxic shock-like syndrome (Table 33.1). The clinicopathologic manifestations and significant morbidity and mortality described with these infections have been linked to the elaboration of two unique exoproteins: edema-producing, or lethal, toxin (LT) and hemorrhagic toxin (HT). Strains with the capacity to produce LT and HT have been associated with puerperal wound infections that are accompanied by anasarca and a clinical picture of septic shock.

The histotoxic clostridia can produce an array of softtissue infections ranging from cellulitis to necrotizing fasciitis to frank myonecrosis.

CLINICAL MANIFESTATIONS

The histotoxic exoproteins manufactured by *C. sordellii* result in localized fascial necrosis and myonecrosis which can mimic gas gangrene. Characteristically, infections occur less than one week postpartum.

Each patient has had a distinctive course characterized by sudden onset of clinical shock marked by severe and unrelenting hypotension associated with marked, generalized tissue edema and 'third spacing' with increased hematocrit, presence of marked leukemoid reaction with total neutrophil counts of 84000/mm^3, 66000/mm^3, and 93600/mm^3, absence of rash or fever, limited or no myonecrosis, and a rapid and potentially lethal course.

Each case has been associated with low grade fever, massive edema, subsequent vascular collapse due to sequestering of the fluid, and a very rapid progression from initial infection to death. Despite what would appear to have been adequate debridement, most patients have died.

Table 33.1 *Clostridium sordellii* syndrome

Sudden onset of clinical shock
Severe **unrelenting shock**
Generalized **edema** progressing to anasarca
Rapid **deterioration** of cardiovascular status
Marked **leukemoid reaction**
Absence of rash or fever

Minimal purulent discharge from infected lesions

Daly JW. *Infect Dis Lttr Obstet Gynecol* 1990; 12:48

Infections with *C. sordellii* are associated with relatively 'clean' incisions; they produce localized tissue damage but a profound exotoxin-mediated systemic response characterized by anasarca, refractory hypotension, and marked leukocytosis. The exotoxins (primarily LT) appear to disrupt the vascular integrity, producing extensive 'third spacing' and, ultimately, cardiovascular collapse.

DIAGNOSIS

An early diagnosis of this or any necrotizing subcutaneous infection based on clinical grounds and an external examination alone can be exceedingly difficult. Consequently prompt surgical intervention is advocated to:

(1) determine the extent and nature of the soft-tissue damage;
(2) remove the source of toxin production and necrotic tissue; and
(3) obtain tissue for histopathologic examination and culture confirmation.

The presence of systemic toxicity and profound, rapidly progressive, widespread edema, leukocytosis, hemo-concentration, and lack of a predominant organism on tissue Gram's stain in the presence of myonecrosis should suggest *C. sordelli* as the potential etiological agent. Confirmation of a presumptive diagnosis is predicated on recovery of this class III anaerobic bacteria.

THERAPY

The management of puerperal infections with this clostridial species has been similar to the treatment of *C. perfringens* myonecrosis: surgical debridement of necrotic tissue, broad-spectrum antimicrobials because of the polymicrobic nature of perineal infections, highdoses of beta-lactam antibiotics, hyperbaric oxygen therapy, and intensive supportive care.

Despite this aggressive therapy, most maternal infections have been fatal. Cardiovascular collapse secondary to marked 'third space' sequestration of fluid has been the cause of death in all instances.

Since debridement and antibiotic therapy do not reverse the chain of events set in motion by the elaboration of toxins in this disease process, the use of exchange transfusion and hyperbaric oxygen should be considered.

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34
Escherichia coli

Escherichia coli is a short, Gram-negative bacillus. Most strains are motile. The organism is a facultative anaerobe and grows readily on most laboratory media, producing a characteristic fetid odor. Serologic identification is based on the antigen specificity of the O antigens. To date, more than 150 group O (somatic cell wall), at least 50 H (flagellar) and a similar number of K (capsular) antigens have been identified. Clinical studies indicate that certain O group antigens are more likely to be incriminated in disease than other strains; this finding suggests a correlation between pathogenicity and antigenic composition. Strains that are rich in K antigens are more resistant to destruction by antibody, complement, and phagocytosis and thus are more prone to circumvent host defense mechanisms than are other strains.

While the gastrointestinal tract is the probable reservoir of organisms, recent studies have documented the existence of significant differences between fecal *E. coli* and those strains isolated from the female genital tract and cases of neonatal sepsis. Cook *et al.* examined 50 *E. coli* isolates from cases of vaginitis, 45 isolates from tubo-ovarian complexes and 45 isolates from infants with neonatal sepsis for selected phenotypic and genetic virulence properties. Results were compared with fecal *E. coli* isolates not associated with disease. A statistically significant greater proportion of *E. coli* associated with infection exhibited D-mannose resistant hemagglutination compared with fecal *E. coli*. This adherence phenotype correlated statistically with the presence of P fimbrae genes.

Selected strains termed enteropathic *E. coli* produce exotoxins. These strains function by either exotoxin production or by their tissue invasive properties which result in bacillary dysentery. Approximately 30–40% of diarrhea observed in United States travelers in developing countries is caused by these strains.

FEMALE GENITAL TRACT INVOLVEMENT

As part of the intestinal and vaginal flora endogenous to man, *E. coli* is pervasive in its pathogenetic spectrum. Within obstetrics and gynecology, it can function as a monoetiologic pathogen to produce urinary tract infection or chorioamnionitis, or the organism can be a lead constituent of polymicrobial infection (i.e. septic abortion, postpartum endometritis, or wound infections). Both monoetiologic and polymicrobial infection may result in septicemia.

URINARY TRACT INFECTIONS

Maternal infection

About 5% of all the serotypes (04, 06, 075, and less frequently 01, 07, 02, and 050) account for almost 75% of *E. coli* urinary tract infections. Irrespective of the route of infection (hematogenous or ascending), the strains that are responsible for infection of the female genital tract almost invariably have as their reservoir the patient's own feces. The prevalence of *E. coli* in feces alone cannot account for its overwhelming predominance as a cause of urinary tract infection. Variables other than merely fecal contamination of the perineum must function to favor the establishment of *E. coli* colonization at the urethral introitus and its subsequent replication in the urine. Since the serotypes of *E. coli* causing acute urinary tract infection are derived from the fecal flora, any factor that alters the predominant fecal serotype of *E. coli* may be of potential clinical significance. When a patient is hospitalized, considerable alterations in strain prevalence of *E. coli* may occur, with the acquisition of new strains, particularly following the use of broad spectrum antibiotics. Once colonization occurs, the new strains persist. The newly acquired strains, having been selected predominantly by prior administration of antibiotics, are more likely to be resistant to multiple antibiotics. The high incidence of strains rich in K antigen in pyelonephritic gravidas suggests that, although initial access to the genital tract may be due to mechanical transfer of *E. coli* by fecal contamination, those K strains, with their enhanced resistance to host defense mechanisms, may possess a greater capacity to invade the kidney. Although the concept of pyelonephritogenic strains of *E. coli* is still controversial, it is probable that antigenic differences among transported strains of *E. coli* may be important in the pathogenesis of urinary tract infections.

Fetal impact

Urinary tract infection in pregnancy may not be without consequences to the fetus. Some evidence suggests that occasionally neonates born to mothers who had urinary tract infections during pregnancy have IgM elevations for which other readily identified causes are not apparent. The concept of *in utero* immunologic stimulation has been reinforced by the demonstration of lymphocyte blast transformation on the part of some neonates whose mothers have had urinary tract infections in pregnancy when their cells are incubated with specific *E. coli* antigens. Whether or not infection of the fetus occurs and is responsible for fetal morbidity is an issue which has yet to be adequately elucidated.

ESCHERICHIA COLI SEPTICEMIA SECONDARY TO ABORTION OR CHORIOAMNIONITIS

Several properties of *E. coli* organisms enhance their ability to function as pathogens. They can replicate both in aerobic and in partially anaerobic environments. Unlike the

majority of bacteria present in the feces and vaginal flora, most strains of *E. coli* are motile. Motility *per se* is not the major determinant of disease. The organisms must be able not only to reach the site of infection, such as the intra-amniotic space or devitalized tissue, but also to replicate successfully. If a strain of *E. coli* has established a persistent pattern of replication in the urinary tract, its ability to produce uterine infection is markedly augmented. When cases of pyelonephritis are excluded, the major factor selecting for septicemia due to the Enterobacteriaceae and *E. coli* in particular is antecedent asymptomatic bacteriuria. The majority of patients with Enterobacteriaceae septicemia for which the uterus is clearly the portal of infection can be demonstrated to have concomitant asymptomatic bacteriuria. The strains of *E. coli* which produce asymptomatic bacteriuria appear to differ from non-nephrogenic isolates obtained from the vagina by virtue of their augmented ability to adhere to cell membranes. With premature rupture of the membranes, effective dissolution of the physiologic and anatomic barrier represented by the cervical mucous plug and intact fetal membranes occurs.

The nephrogenic *E. coli* concomitantly sustained within the vaginal flora now obtain potential access. Access to amniotic fluid does not necessarily correlate with ensuing infection unless the bacterium in question is an exogenous pathogen (i.e. group A streptococci, *Neisseria gonorrhoeae*, or an endogenous bacteria for which augmented virulence has been preselected). Once the organism either overwhelms the infant's defense mechanisms at the alveolar level or penetrates the chorioamnion of the placenta, fetal infection is initiated. Maternal infection is observed when the disease process extends through the placental tissue and reaches the maternal vascular channels at the implantation site. When infection due to *E. coli* is associated with retained products of conception, septicemia may occur. In contrast to most infections in which access to a vascular space occurs, the placental site cannot be completely thrombosed. The situation is analogous to a patient who receives an IV infusion of a potentially unlimited quantity of bacterial organisms. The focus of therapy is surgical removal of the source of organisms while instituting supportive measures to sustain the gravida. It is imperative that the antibiotic therapy be such that the divergent spectrum of Enterobacteriaceae is more than adequately covered. In the management of retained products of conception and criminal abortion, there is not one but a multitude of potential or functional pathogens; hence the necessity for broad-spectrum antimicrobials that will destroy both Gram-positive and Gram-negative organisms. With prolongation of the disease process, anaerobic organisms have a progressively larger representation in the pathogenetic flora, and there is a greater tendency for anaerobic streptococci and *Bacteroides* to predominate and gain access to the maternal intravascular space.

WOUND INFECTIONS

E. coli is not an infrequent isolate from infected wounds. Rarely is it isolated in pure culture. While it is important in initiating the disease, one almost never sees progressive wound infections and resulting septicemia due to *E. coli per se*. Once an appropriate anaerobic oxidation-reduction potential is achieved, the more obligatory anaerobes, such as anaerobic streptococci and *Bacteroides*, emerge as the dominant organisms in the

wound. Therapy directed against *E. coli* in the absence of early abscess formation may be effective in aborting the progression of the local process. In contrast to *E. coli* isolates from the patient with primary pyelonephritis, a higher incidence of organisms with resistance to broad-spectrum antibiotics is encountered.

POSTPARTUM ENDOMETRITIS

Barring obstetrical trauma or retained products of conception, postpartum endometritis following spontaneous vaginal delivery occurs in 2–3% of gravida. In the great majority of patients, an exogenous pathogen can be isolated from the endometrium. In selected instances, a member of the Enterobacteriaceae can be isolated as the quantitatively dominant bacteria amidst a polymicrobial background. The majority of these patients have concomitant asymptomatic bacteriuria. The probability of ensuing postpartum endometritis due to *E. coli* is markedly enhanced when chorioamnionitis due to the bacteria in question anteceded parturition. When a woman is delivered by cesarean section, the need for a virulence factor to select for pathogenicity is obviated. In this setting the Enterobacteriaceae can function as part of the anaerobic progression. *E. coli* is more prone to exhibit gas formation in the course of soft tissue infection in diabetics. All that is crepitant is not *Clostridium perfringens* but one is committed therapeutically to use a regimen effective against both organisms until a definitive bacteriologic diagnosis has been established.

THERAPY

Generally, the major consideration in the therapy of urinary tract infections (Chapter 68), abortion (Chapter 64), chorioamnionitis (Chapter 60), and wound infections (Chapter 77) is whether the pathogenic strain of *E. coli* was acquired from the hospital or from a nonhospital environment. The acquisition of infection in the former milieu or infection in a patient who had received prior antibiotic therapy argues for the selection of an aminoglycoside or a fluoroquinolone.

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35
Gardnerella vaginalis (Haemophilus vaginalis)

Gardnerella vaginalis is a facultative, anaerobic, pleomorphic, non-motile, Gram-variable bacillus or coccobacillus. Characteristically on Gram stain, they tend to be arranged at angles or parallel to one another. Morphologically, when grown on appropriate media, the colonies appear as minute, convex, circular, translucent 'dew drops' measuring about 0.1–0.8 mm in diameter. Gram-negativity is characteristic of the organisms from early, 6 to 36 hour-old cultures. After 72 to 96 hours, the organism may stain Gram-positive.

Gardnerella vaginalis is one of the most important regulators of the abnormal vaginal flora. Only two bacteria, *Lactobacillus* species and *G. vaginalis* have been shown to be recoverable as sole isolates from the female genital tract. What is implied by this finding is that they can individually function as ultimate regulators of the female genital tract's bacterial flora. Chaisilwatana and Monif have documented the *in vitro* ability of *G. vaginalis* to inhibit *Lactobacillus* species and vice-versa. *In vivo* analysis of microbiological data has shown the absence of aerobic lactobacilli when *G. vaginalis* is present at high multiplicity.

TAXONOMY OF *GARDNERELLA VAGINALIS*

The original assignment of Leopold's bacillus to the genus *Haemophilus* was predicated upon the assumption that bacteria required X (heme) and Y (nicotinamide adenine dinucleotide) factors for its growth. The name *Haemophilus vaginalis* was used from 1955–1961, at which time LaPage demonstrated that neither the heme nor the nicotinamide adenine dinucleotide was essential for its replication, and suggested that *Haemophilus vaginalis* might belong to the genus *Corynebacterium*. In 1963, Zinnemann and Turner concluded that the bacterium was not Gram-variable but Gram-positive and proposed the specific name of *Corynebacterium vaginalis*. Despite the opposition of microbiologists such as Washington, Greenwood and Pickett, the proposed name gained wide acceptance. Bergry's Manual of Determinative Bacteriology retained the name *Haemophilus vaginalis*. The major reason for not adopting the widely publicized new name of *Corynebacterium vaginalis* was the fact that the bacteria was clearly not a *Corynebacterium*. *Corynebacterium* are catalase-positive, have arabinose in the cell wall, have a significant guanine-cystosine content and serologically agglutinate with themselves. Finally, Greenwood and Pickett proposed that Leopold's bacillus be placed in a new genus appropriately termed *Gardnerella* and that the specific organism be called *Gardnerella vaginalis* in honor of Herman Gardner.

GARDNERELLA VAGINALIS VULVOVAGINALIS

The alterations in the microbiological flora of the female genital tract required to produce infection and its translation into disease have been poorly delineated. On a theoretical level, the governing monoetiological concept of the disease (a given bacterium causing a specific disease state) has contributed to a limited perspective of the biological interrelationships and interdependencies governing the various individual constituents of the microbiological flora of the female genital tract.

The relationship of *G. vaginalis* to disease is not simply a cause-and-effect phenomenon. *G. vaginalis* is a common constituent of the vaginal flora of women undergoing elective vaginal hysterectomy or with abnormal Papanicolaou smears, yet only a relatively small percentage of these women are symptomatic or have a clinically significant vaginal discharge. *G. vaginalis* has been shown to be a constituant of the vaginal flora of women who consulted a student health center and who were free of clinically overt disease.

The difference between colonization and disease appears to be a partial function of the magnitude of bacterial replication. Quantitative bacteriological studies have shown that disease, when due primarily to *G. vaginalis,* is associated with greater than 10^8 colony forming units (cfu) per gram of vaginal fluid. If re-infected post-therapy by an untreated sexual consort, the patient is usually asymptomatic; however, in this setting the quantitative counts are less than 10^6 cfu per gram of vaginal fluid. For disease to occur, not only must there be an environment which will sustain *G. vaginalis* as a constituent of its microbiological flora, but something must happen to free the bacteria from the inhibitory restraints which govern the magnitude of its replication.

Gardnerella vaginalis functions as a pathogen under selected circumstances. Part of the controversy concerning *Gardnerella* vulvovaginitis has been engendered by the failure to distinguish monoetiological disease due to *G. vaginalis* from mixed infection in which *G. vaginalis* may be the predominant aerobic bacteria, but functioning in concert with a polymicrobial anaerobic flora.

Monoetiological disease-type I

What Gardner and Dukes initially described was a clustering of specific signs and clinical findings. The typical patient presents with a malodorous, grey, homogeneous vaginal discharge whose pH is greater than 5.0. The microscopic picture produced is characteristic. Gram stain will show a large number of Gram-variable small coccobacilli which give a salt and pepper appearance and possibly ‘clue cells’. ‘Clue cells’ are vaginal epithelial cells which have a stippled appearance owing to the almost uniformly spaced coccobacilli. The wet mount shows a literal sea of coccobacilli often appearing as rafts or clumps of bacteria floating between epithelial cells. Polymorphonuclear leukocytes are characteristically absent, or if present they are in insignificant numbers. The coccobacilli dominate all fields of the slide, usually in a ratio exceeding 100:1 of other bacteria. Gram-stained smears reveal the overwhelming dominance of genus as determined by organismal morphology.

Polymicrobial disease-type II

The concomitant presence of a large number of pus cells is most commonly associated with a mixed polymicrobial bacterial infection. Larsson *et al.* demonstrated that 36.5% of women with bacterial vaginosis (BV) had vaginal leucocytosis. Their study indicated that women with BV had similar sexual behavior to women at risk for sexually transmitted diseases (STD). Peters *et al.* analyzed BV in women with dyskaryotic PAP smears. The presence of BV was significantly associated with age of first intercourse, the lifetime number of sexual partners and current *Chlamydia trachomatis* infection. Over 37% of women attending STD clinics have BV. Josoef *et al.* identified a 23.3% prevalence of a major STD among pregnant women with BV, chlamydial infection being the most common. Anywhere from 19–48% of patients with *Trichomonas vaginalis* vulvovaginitis will have *G. vaginalis* concomitantly isolated. Patients with gonococcal endocervicitis or acute salpingitis will frequently have *G. vaginalis* as a co-isolate or as a constituent in the anaerobic progression.

Type II disease is more than a specific disease entity, it is a marker for the possible presence of a significant STD pathogen. In addition, endocervical and/or vaginal colonization by *G. vaginalis* has been shown to be a risk factor for the development of post-hysterectomy cuff cellulitis.

The ability of metronidazole to eradicate *G. vaginalis* (which lacks the required nitroreductase system necessary for the drug to function as an antimicrobial agent) has supported the hypothesis that the principal effect of therapy may not be directly on *G. vaginalis* but rather on the anaerobic co-constituents of the vaginal flora. It has been postulated that anaerobic bacteria may provide some undefined factors to support the growth of *G. vaginalis* and that the inhibition of anaerobes may be the critical factor in the bacteriological eradication of the organism. *Prophyromonas melaninogenicus* and *Bacteroides fragilis* have been shown to inhibit phagocytosis of selected bacteria by leukocytes; however, the degree of inhibition appears to be species related.

Most infections from which *G. vaginalis* is isolated are due to a synergistic interaction of the bacterium with other bacterial or protozoan constituents of the vaginal flora. Quantitatively, bacterial replication is on the order of 10^9 logs of bacteria per gram of vaginal fluid. The vaginal pH is in excess of 4.5. Wet mounts reveal the presence of bacteria, which may or may not be associated with significant bacterial adherence to squamous epithelial cells and numerous polymorphic neutrophils. Addition of a drop of 10% potassium hydroxide (KOH) to the wet mount will result in a ‘fishy odor’ (positive amine test).

GARDNERELLA VAGINALIS AS A SYSTEMIC PATHOGEN

Until 1974, the role of *G. vaginalis* as a systemic pathogen was controversial. Prior to that time most microbiologists discounted the bacteria’s ability to function as a systemic pathogen. Blood cultures harboring *G. vaginalis* were not infrequently discarded. Monif and Baer were the first not only to focus on the validity of hematologically derived isolates, but also the ability of this organism to function as a constituent in the anaerobic

progression of patients with endometritis and endomyometritis. These investigators noted that, while a common isolate from obstetrical patients, *G. vaginalis* was a rare isolate from the intravascular compartment of gynecological patients. A subsequent series by Venkataramani and Rathburn of 29 patients with *G. vaginalis* bacteremia corroborated these earlier findings. Nineteen of the isolates were derived from postpartum women and six from patients with septic abortion.

While a monoetiologic septicemia due to *G. vaginalis* does occur, the organisms are more commonly recovered from the intravascular compartment with other facultative anaerobes. The most prevalent co-isolates in these polymicrobial bacteremias include the peptococci, peptostreptococci, *Bacteroides*, and coagulase-negative staphylococci.

G. vaginalis septicemia develops in the context of three clinical settings:

(1) septic abortion;
(2) postcesarean section endomyometritis; and
(3) postpartum endometritis.

In those instances where *G. vaginalis* is the sole pathogen isolated from the blood, the patients develop significant pyrexia; however, leukocytosis may not be present. Not infrequently, residual products of conception are present within the endometrial cavity. Clinical amelioration with rapid defervescence of fever occurs with their removal and conventional antibiotic administration. *G. vaginalis* is an organism of low pathogenicity and as a monoetiological pathogen does not produce significant morbidity and mortality.

In cases of polymicrobial bacteremia, particularly that due to postcesarean section endomyometritis, the pathogenicity of the multiple organisms appears to be additive. Therapy should be directed against all bacteria which can participate in the anaerobic progression. The low pathogenicity of *G. vaginalis*, combined with its apparent sensitivity to the drugs commonly used in obstetrics, renders its therapeutic management relatively simple.

Gardnerella vaginalis, on rare occasions, may be a cause of perinatal septicemia in the immediate neonatal period following maternal chorioamnionitis. The bacteria attain access to the fetus through ascending infection associated with premature rupture of the fetal membranes. Even in the absence of therapy, it is uncommon for significant neonatal morbidity to ensue.

INTER-RELATIONSHIP OF *GARDNERELLA VAGINALIS* AND VAGINAL BACTERIOSIS (BACTERIAL VAGINOSIS)

Bacterial vaginosis (or more properly termed, vaginal bacteriosis; bacterial vaginosis means bacteria having an excess of vaginas) is due to an imbalance in the bacterial ecosystem of the female genital tract. Qualitatively, the lactobacilli are replaced by a mixture of predominantly anaerobic organisms (*Bacteroides*, *G. vaginalis*, *Mobiluncus*, *Mycoplasma hominis*, peptostreptococci). Quantitatively, the concentration of these bacteria, when present, increases 100x from 10 million bacteria per ml of vaginal fluid to 1 billion bacteria per ml of vaginal fluid.

Vaginal bacteriosis is a syndrome characterized by:

(1) homogeneous discharge;

(2) vaginal pH>4.7;
(3) positive amine odor test;
(4) presence of ‘clue cells’; and
(5) demonstration of anaerobic bacterial overgrowth.

Type II *Gardnerella* vulvovaginitis does result in vaginal bacteriosis but vaginal bacteriosis is not necessarily type II *Gardnerella* vulvovaginitis. *G. vaginalis* is isolated from only 83–87% of vaginal samples obtained from women with vaginal bacteriosis.

DIAGNOSIS

The clinical diagnosis of vaginal bacteriosis necessitates the presence of 3 of the 4 following criteria:

(1) presence of milky discharge;
(2) vaginal pH≥4.7;
(3) presence of ‘clue cells’; and
(4) amine odor after the addition of KOH.

Vaginal Gram smear can infer the diagnosis by demonstration of:

(1) relative absence of lactobacilli;
(2) presence of an abnormal bacterial flora;

a. qualitatively
b. quantitatively; and

(3) presence of ‘clue cells’.

The presence of ‘clue cells’ is the best single diagnostic indicator of vaginal bacteriosis. Since the bacterial constituents producing disease can vary significantly, vaginal cultures are difficult to interpret.

The discharge of vaginal bacteriosis may be present on the perineum. It usually involves the anterior and lateral walls of the vagina.

The characteristic ‘fishy’ vaginal odor is a clue to increased amine production by anaerobic bacteria. Intensification of this odor by adding 10% KOH to vaginal secretions is due to conversion of amines to a more volatile state. Amine odor is the most specific indicator of disease but lacks sensitivity.

THERAPY

A number of therapeutic regimens have been effective for type II disease (vaginal bacteriosis):

(1) oral metronidazole: 500 mg bid for 7 days (efficacy=85%);
(2) oral clindamycin: 300 mg bid for 7 days (efficacy=85%);

(3) intravaginal 2% clindamycin cream: 5 ml applied intravaginally at night for seven days (efficacy=85%);
(4) metronidazole gel: 5 ml of 0.75% gel inserted intravaginally twice daily for 5 days; and
(5) amoxycillin 500 mg tid x 5–7 days.

When dealing with type I disease, good results have been achieved with:

(1) amoxycillin 500 mg tid x 5–7 days;
(2) doxycycline 100 mg bid x 4 days; or
(3) clindamycin 300 mg bid for 7 days.

Most therapies for BV achieve an initial 75–85% clinical success; however microbiological success a month or so post therapy is between 50 and 60%, if that. The reasons for both therapeutic failures and extented microbiological failures have not been well delineated. Individual strains of *G. vaginalis* are not susceptable to metronidazole. A second important therapeutic variable is the presence of *Mobiluncus* species within the BV flora. *Mobiluncus* species are resistant to metronidazole. Depending on whether *M. curtisii* or *M. mulieris* is present, clindamycin may not afford optimal coverage. To address these possibilities, the European use combine metronidazole and erythromycin therapy.

All women with BV need a comprehensive evaluation for co-infections, particularly the major STDs. While most male sexual partners are colonized with BV-type flora, studies to date have yet to conclusively demonstrate increased efficacy when sexual partners are treated. Gardner and Duke isolated *G. vaginalis* from the urethra of 54 (96%) of 57 husbands of women with *G. vaginitis*, but not from the urethra of 20 medical students. The urethra of 77–91% of the sexual consorts of infected women can be demonstrated to harbor the bacteria. These male carriers rarely have clinical evidence of disease. Women whose sexual consorts are not treated tend to become reinfected. If reinfection occurs, ampicillin or amoxycillin is superior to bolus metronidazole in the treatment of the sexual consort.

BV AND PRETERM DELIVERY

A causative relationship between vaginal bacteriosis and preterm labor delivery has been inferred from the Vaginal Infection and Prematurity Study, which involved 10397 pregnant women from seven medical centers who had no known risk factor for preterm delivery of low-birth weight infants. In a subsequent study, Hauth *et al.*, using metronidazole and erythromycin, reduced the rates of premature delivery in women with bacterial vaginosis and an increased risk for preterm delivery. Similar results were achieved by McGregor *et al.* In the prospective arm of the McGregor study, the presence of bacterial vaginosis was associated with increased risks of pregnancy loss, preterm premature rupture of the membranes, and preterm birth. When gravida with bacterial vaginosis were treated with orally administered clindamycin, a 50% reduction in premature rupture of the membranes occurred. Subsequent studies have suggested that prophylactic screening and therapeutic intervention for abnormal vaginal flora may be of value when limited to a high risk subpopulation rather then all women. Irrespectively,

when BV is diagnosed, and especially if inflammatory cells are present, effort should be directed at not only eradicating symptomatology, but also eliminating the possibility of co-functioning STDs.

BV AND ACUTE SALPINGITIS, ECTOPIC PREGNANCY AND SECONDARY INFERTILITY

A number of cross-sectional, static group studies have proposed a causal relationship between BV and pelvic inflammatory disease, ectopic pregnancy, cervical cancer, retrovirus infection (AIDS) and secondary infertility. Most of these studies have centered on women with high risk factors for STDs. Multiple studies of women with BV have revealed a high incidence of co-infection with major STD pathogens, and in particular *Chlamydia trachomatis*. Larsson *et al.* analyzed the sexual behavior of 400 women with and 400 women without BV. Their study indicated that women with BV had similar sexual behavior to women at risk for STDs. In the Swedish Women's Health Study, no significant differences in sexual activity risk factors existed when women with BV were compared with women with endocervical *C. trachomatis* except for a higher frequency of casual sex. Other studies have demonstrated a significant prevalence (37.8%) of BV in women attending STD clinics and frequent co-infection with a major STD.

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36
Klebsiella/Enterobacter

Like *Escherichia coli, Klebsiella* and *Enterobacter* belong to the genus Enterobacteriaceae, but are grouped under the tribe *Klebsiella*. They are colonizers of the human gastrointestinal tract.

KLEBSIELLA

On Gram stains, *Klebsiella* appears as a large Gram-negative rod. Owing to its prominent polysaccharide capsule it forms large mucoid colonies on agar media. Serotyping is done using predominantly the K capsular antigen. More than 70 K types have been identified. Although the capsule is an important virulence factor in preventing phagocytosis and helping to retard leukocyte migration, no specific K type is more pathogenic than another. Like most Enterobacteriaceae, *Klebsiella* produces endotoxin. The predominant species within obstetrics and gynecology is *Klebsiella pneumoniae*. Other species tend to be lumped together and reported just as *Klebsiella* species.

Clinical manifestations

As a monoetiological pathogen, *K. pneumoniae* functions as an important agent in urinary tract infection, chorioamnionitis, perinatal septicemia, and endometritis. When it functions as part of the anaerobic progression, it may be a constituent of a polymicrobial endomyometritis or the lead organism in a ruptured tubo-ovarian complex.

The incidence of disease is approximately 1/10 that due to *E. coli*. Clinically disease due to *Klebsiella* species is identical to that described for *E. coli*.

Therapy

The *Klebsiella* are almost invariably resistant to all the penicillins. The drugs of choice for the *Klebsiella* are the cephalosporins, in particular the third generation cephalosporins.

ENTEROBACTER

Enterobacter consists primarily of *E. aerogenes, E. cloacae*, and *E. agglomerans*. Unlike *Klebsiella*, *Enterobacter* organisms are motile and tend to be less heavily encapsulated. They do not produce H_2S on triple sugar iron medium, are indole- and methyl red-negative, use citrate as a sole carbon source, and can ferment lactose. Simplified tests for

decarboxylation of the diamino acids lysine, arginine, and ornithine differentiate *E. cloacae, E. aerogenes, E. agglomerans, and K. pneumoniae.*

The pathogenic spectrum is comparable to that described for *Klebsiella*. Their disease prevalence is 1/10 that observed with *Klebsiella* but it is of greater clinical significance owing to the resistance of *Enterobacter* to many of the penicillins and to all first-generation cephalosporins and some of the second- and third-generation cephalosporins. This lack of susceptibility to the commonly used antibiotics in obstetrics and gynecology underlies the importance of this group of bacteria.

Clinical manifestations

Enterobacter cloacae is a significant cause of hospital-acquired infections, along with *E. agglomerans*. These organisms are capable of horizontal spread in the hospital environment and, like many opportunistic Enterobacteriaceae, can be spread on the hands of hospital personnel.

The three clinical areas in which the *Enterobacter* function as significant pathogens in obstetrics and gynecology are:

(1) nosocomial infections;
(2) urinary tract infection; and
(3) maternal and perinatal septicemia/meningitis.

Enterobacter cloacae is the species most frequently associated with nosocomial infections. Within a hospital setting, *Enterobacter* organisms can establish widespread colonization of patients and as such represent an ongoing threat by a multi-resistant bacteria to a vulnerable patient population.

The association of *Enterobacter* with contaminated intravenous fluids is somewhat predictable considering its aquatic lineage. *Enterobacter* species as the sole pathogen in the majority of blood cultures should suggest the possibility of parenteral introduction of *Enterobacter* contaminated fluid or the presence of significant urinary tract infection.

Although all *Enterobacter* species are capable of causing disease, the three primary nosocomial pathogens are *E. aerogenes, E. cloacae,* and *E. agglomerans*.

The *Enterobacter* produce a spectrum of infection and/or disease of the genitourinary tract which is very similar to that induced by *E. coli*. The *Enterobacter* are the etiological agents for approximately 1 % of the cases of asymptomatic bacteriuria but 5% of the cases of pyelonephritis. This discrepancy is due to the failure to eradicate asymptomatic bacteriuria when identified. Most of the antibiotics used to treat urinary tract infection are ineffective against most *Enterobacter* species. The failure to eradicate asymptomatic bacteriuria is the failure to prevent pyelonephritis.

Asymptomatic bacteriuria provides a reservoir of Gram-negative aerobic bacteria of increased virulence within the vaginal flora. With prolonged rupture of the fetal membranes, the nephrogenic strains of *Enterobacter* ascend into the amniotic cavity from where they may induce chorioamnionitis, maternal septicemia, and/or perinatal septicemia. A woman with asymptomatic bacteriuria due to the Enterobacteriaceae has an eightfold increased probability of endometritis following vaginal delivery.

Therapy

The first generation cephalosporins classically have little or no inherent anti-*Enterobacter* activity. Antimicrobials which have a high degree of activity against the *Enterobacter* are the third generation cephalosporins, the fluoroquinolones, and the aminoglycosides. As in the case with *Klebsiella,* there have been increasing reports of aminoglycoside-resistant *Enterobacter* strains from across the country. In such situations, amikacin has remained the preferred aminoglycoside.

In the treatment of uncomplicated urinary tract bacteriuria, the carboxypenicillins and nalidixic acid have activity against most *Enterobacter* species. Nitrofurantoin is reliable only against *E. agglomerans.*

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37
Mobiluncus species

Sheldon M.Gelbert, PhD, and Jessica L.Thomason, MD

Mobiluncus is a non-spore-forming, anaerobic, curved rod-shaped bacterium that has been isolated most frequently from the lower genital tract of women. The organism was first isolated and described by Curtis in 1913, and first classified, albeit erroneously, by Prevot in 1940. Prevot named the organism *Vibrio mulieris* and located it taxonomically within the group of anaerobic vibrios. In 1984, Spiegel and Roberts reclassified the organism since this organism was not found to fit into the *vibrio* group nor did its description fit that of any other existing genus. Vibrios have Gram-negative type cell walls, produce cytochrome oxidase, and are motile by polar flagella. Curved anaerobic rods possessed none of these traits and DNA homology between *Mobiluncus* and other existing genera was less than 1%. Accordingly, they created a new genus, *Mobiluncus* in the family Bacteroidaceae. They established two species, *M. mulieris* and *M. curtisii*, and divided *M. curtisii* into two subspecies, *M. curtisii* subspecies *curtisii* and *M. curtisii* subspecies *holmesii*.

Mobiluncus has the cell wall structure and biochemical composition of a Gram-positive rod, but it usually stains Gram-negative. Electron micrographs reveal a multilayered cell wall consisting of a trilaminar structure with a peptidoglycan layer which lacks an outer membrane. This cell wall structure is similar to that seen in *Gardnerella vaginalis*. The thinness of this peptidoglycan layer may explain the tendency of these organisms to stain Gram-negative. However, because its cell wall lacks an outer membrane this organism is considered to be Gram-positive.

FEMALE GENITAL TRACT INVOLVEMENT

Clinical manifestations

Mobiluncus species have been closely associated with bacterial vaginosis and are considered by some investigators to be an etiological agent of that syndrome. The organism can be detected in about 50% of patients with bacterial vaginosis either by its characteristic serpentine or corkscrewing pattern of motility on direct microscopic examination (wet mount) of vaginal secretions, or as Gram-variable curved rods with tapered ends on Gram stain. Culture methods have not proven reliable. Selective and differential media that work well on laboratory isolates have yet to be found clinically useful. In fact, even when the organism is the predominant morphotype on Gram stain, it often cannot be recovered by culture methods. The findings of *Mobiluncus* in a wet mount or on Gram stain strongly correlates with the concomitant presence of vaginal bacteriosis.

Mechanisms of pathogenicity for *Mobiluncus*, if any, have not been elucidated. The organism produces large quantities of succinate which has been shown to decrease both chemotaxic response and phagocytic activity in leukocytes and to stimulate the growth of specific anaerobes, e.g. *Bacteroides melaninogenicus*. These factors may play a role in bacterial vaginosis. *Mobiluncus* has also been isolated in mixed culture from extra-genital wounds and abscesses and in pure culture from repeat blood cultures. *Mobiluncus* species have been isolated from patients with pelvic inflammatory disease and have been isolated from amniotic fluid.

Although never cultured from males, *Mobiluncus* has been detected by genetic probe analysis and by Gram stain in prostatic and seminal secretions in partners of patients with vaginal bacteriosis. It is, therefore, suspected that males serve as reservoirs for this organism. *Mobiluncus* has not been incriminated in any diseases in males.

Diagnosis

On Gram stain, *Mobiluncus* appears as curved rods with tapered ends occurring singly or in pairs, sometimes with a gull wing appearance or as semi-circles. It produces tiny punctate colonies about 1.2 mm in diameter on blood agar after 3–5 days anaerobic incubation at 35ºC. It does not pit or corrode the agar. Although growth requirements are incomplete, *Mobiluncus* can be grown on nutrient agar supplemented with blood or serum, or in carbohydrate broth enriched with 2% inactivated serum. It is not hemolytic on fresh blood but appears hemolytic on very old (4–6 weeks) rabbit and human blood. All strains can produce acetic, lactic and large amounts of succinic acids from a variety of carbohydrates. They produce no detectable catalase or cytochrome oxidase, but can hydrolyze starch. They are motile by a tuft of flagella originating in the concave aspect of the bacterium. *M. mulieris* is longer, about 3–5 μm, than *M. curtisii*, which is about 1.5 μm in length. Both species are about 0.4 μm in width. *M. curtisii* can hydrolyze hippurate, decarboxylate arginine and split galactosides. *M. mulieris* is negative for all of these traits. *M. mulieris* always stains Gram-negative while *M. curtisii* can stain Gram-positive.

The two species can also be differentiated by antimicrobial susceptibility patterns. *M. curtisii* is resistant *in vitro* to nitroimidazole agents, while *M. mulieris* is generally sensitive.

Therapy

All strains are resistant *in vitro* to colistin, nalidixic acid, and aminoglycosides, and sensitive *in vitro* to penicillin and erythromycin, further demonstrating that these organisms have cell walls that more closely resemble those of Gram-positive organisms. The presence of a *Mobiluncus* species isolate in a patient with vaginal bacteriosis accounts for the 15–20% failure rate observed with metronidazole treatment. The demonstration of *Mobiluncus* warrants the addition of erythromycin to the therapeutic regimen.

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38
Peptostreptococci

In 1893, Veillon first described what is today recognized as the anaerobic *streptococcus*. He recovered a strict anaerobic *streptococcus,* which he called *Micrococcus foetidus,* from a case of suppurative bartholinitis. The anaerobic streptococci are Gram-positive cocci that grow in chains, clumps, pairs, or even tetrads. Because of the extent of heterogeneity within the group, there is no characteristic pattern of fermentation. With the exception of the micro-aerophilic group, the peptostreptococci do not produce beta-hemolysis. Because of their proteolytic properties, the bacteria often produce large amounts of hydrogen sulfide from sulfur-containing amino acids, resulting in a putrefactive odor. Taxonomically, the peptostreptococci and the peptococci have recently been grouped together under the peptostreptococci. Because of the similarity of their pathogenic spectrum, the clinical distinctions between the two had never been sharply delineated. Morphologically, the peptococci are distinct from the peptostreptococci and are more properly thought of as the anaerobic staphylococci. They are larger than the peptostreptococci and, rather than aggregating in chains, tend to form clusters similar to their more aerobic counterparts.

FEMALE GENITAL TRACT INVOLVEMENT

The peptostreptococci constitute part of the natural flora of humans. The presence of these organisms within the vaginal and alimentary tracts readily favors their conversion from commensal organisms to opportunistic pathogens. The peptostreptococci have been implicated in many infections, including chronic ulcers, the anaerobic form of gangrene, pelvic abscesses, septic abortion, pyogenic liver abscesses, septicemia, urinary tract infection, and subacute bacterial endocarditis. However, the disease entities affecting the female genital tract are often examples of synergistic bacterial growth. In its original definition by Meleney, bacterial synergism was described as not being a phenomenon in which one organism initiates a process and another takes over, but rather one in which there is a necessity for organisms to grow together intimately, implying the cross-utilization of intermediary products of metabolism. Peptostreptococcal infections in obstetrics and gynecology that deserve special attention include endometritis and septicemia, and progressive synergistic bacterial gangrene.

Endometritis and septicemia

As early as 1910, peptostreptococci had been isolated from cases of puerperal sepsis. The prerequisite for infection is a low oxidation-reduction potential, such as that provided by grossly traumatized or devitalized tissue. Not infrequently a synergistic relationship

exists with either *G. vaginalis* or the Bacteroidaceae. The *G. vaginalis*-peptostreptococci coinfection occurs more frequently in obstetric patients, whereas the *Bacteroides*-peptostreptococci are more common synergistic pathogens in gynecologic patients. Given the conditions permitting anaerobic growth, the initial infection is endometritis. The signs of infection include a foul-smelling lochia which is usually followed by pyrexia. If infection is the consequence of retained septic products of conception, the process spreads through the partially thrombosed sinuses at the placental site and gains access to the uterine and ovarian veins. The process may not progress beyond this point, with resolution of the infection occurring gradually over several weeks.

In uncontrolled infection, more widespread thrombophlebitis occurs (Figure 38.1). The process may involve the iliac veins, inferior vena cava, and left renal vein. Frequently the thrombosis is discontinuous, so that both external iliac veins may be involved, whereas the

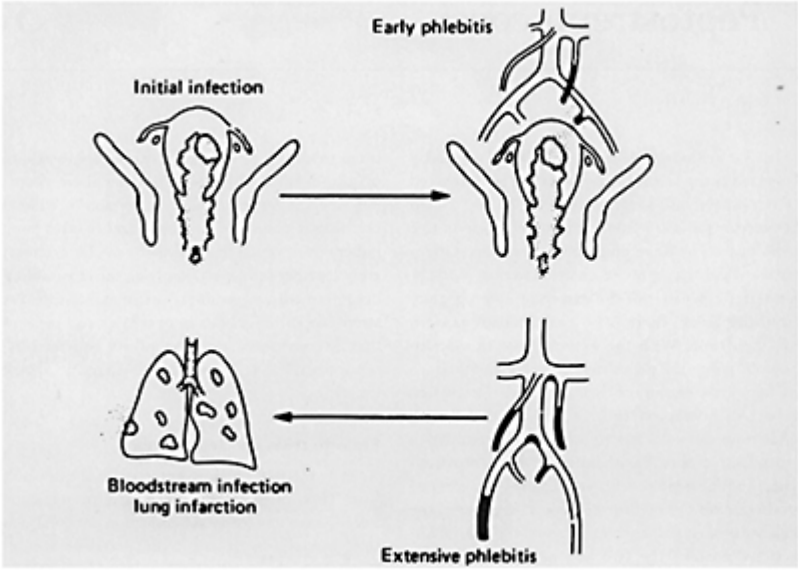

Figure 38.1 The uncontrolled spread in infection due to the peptostreptococci. Frequently associated with severe injuries to the birth canal and with retained pieces of placenta, the infection is initially limited to these injured areas. Organisms tend to spread in the clot within thrombosed sinuses to the uterine and ovarian veins. Later more widespread thrombophlebitis may

> involve the iliac veins, inferior vena cava, and renal vein. From these foci septic emboli slough off,causing intermittent septicemia and abscesses in the lung. (Gibberd GF. *J Obstet Gynaecol Br Commonw* 1966; 73:1)

common iliac veins remain patent. Septicemia is almost inevitable with extensive phlebitis of the pelvic veins. Its severity is influenced by the presence of a copathogen. Immediate sequelae of the bacteremia include implantation of the anaerobic streptococci on a previously damaged heart valve or hepatic localization in conjunction with a *Bacteroides* species, resulting in subacute bacterial endocarditis or hepatic abscess, respectively. The late sequelae of this disease process include septic embolization and the resultant abscess in the lungs and/or pulmonary infarcts. Septicemia associated with thrombophlebitis is characterized by repetitive sudden febrile spikes, which lend a characteristic profile to the temperature chart. At necropsy, wide-spread pelvic thrombophlebitis and multiple lung abscesses are frequent findings. The morbidity and mortality seen with *Bacteroides*-peptostreptococci is far more significant than that observed with *G. vaginalis*-peptostreptococci alone.

Antibacterial therapy is best directed against both components in the synergism, although it is possible the eradication of one of the two organisms and the surgical removal of the conditions favoring anaerobic growth will allow the condition to resolve itself. Penicillin, the drug of choice in the treatment of the peptostreptococci, is often ineffective in eradicating *B. fragilis*. The presence of thrombophlebitis is an indication for heparinization.

Progressive bacterial synergistic gangrene

In 1926 Meleney first described a condition which he later termed ‘progressive synergistic gangrene’, which was due to beta-hemolytic, microaerophilic streptococci in synergism with other organisms (e.g. *Staphylococcus aureus, Proteus,* etc). The disease process usually begins around retention sutures after abdominal surgical repairs. The initial lesion is a small, very painful, superficial ulcer which gradually spreads. The central shaggy ulcerated area is surrounded by a rim of gangrenous skin. This in turn is surrounded by an outer zone of peripheral erythema that infiltrates the adjacent pink edematous skin. The condition is distinct from the fulminating ulcer described by Meleney that is associated with group A hemolytic streptococci and which occurs without the synergistic action of other organisms. Meleney reproduced this lesion experimentally with a mixture of microaerophilic anaerobic streptococci and *S. aureus*. If pure cultures of either organism were used, gangrenous ulcers did not develop. It should be noted that even in the preantibiotic period, this was a rare disease.

Therapy involves massive systemic administration of antibiotics, including penicillin, with a wide incision of the lesion. Conservative treatment has resulted in repetitive operations. The incisional line must go far beyond the area of redness and edema and bleed readily.

DIAGNOSIS AND THERAPY

The diagnosis and therapy of peptostreptococcal disease is that discussed under Anaerobic infections (Chapter 3).

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39
The *Proteus* group

The *Proteus* organisms are motile Gram-negative bacilli which exhibit significant variation in size and shape. Young cultures grown on solid agar are particularly pleomorphic. Short coccobacillary and long filamentous forms may be identified in cultures and exhibit rapid spread over the entire surface of the culture. Such 'swarming' is due to the organism's very active motility. The spread is so rapid that, not infrequently, the presence of a *Proteus* strain as a component in a specimen may mask the presence of another pathogen. Such specimens should be reisolated by cultivation on relatively dry surfaces of 5% agar or on ordinary 1–2% agar containing 0.1% chloral hydrate. Urease production is characteristic of the *Proteus* group. Experimental evidence suggests that urease production may preferentially enhance bacterial replication within the renal medulla, once infection is established. While urease production is a distinguishing metabolic characteristic, functional subdivision of the *Proteus* group is based on maltose fermentation and indole formation. The maltose-fermenting strains form indole; those that do not ferment maltose are indole-negative. The relative ability or inability to form indole is important in antibiotic chemotherapy. Indole-positive strains, such as *Proteus vulgaris*, are resistant to ampicillin, whereas most of the indole-negative strains, such as *Proteus mirabilis*, are highly susceptible.

IMMUNOLOGY OF INFECTION

Motile strains of *Proteus* contain H (flagellar) antigens in addition to the somatic O antigens. Certain strains of *P. vulgaris* labeled OX share specific polysaccharide antigenic determinants with *Rickettsia prowazekii* (the organism of epidemic typhus) and other rickettsiae. The serologic cross-reactivity of the OX strains with certain rickettsial organisms has resulted in the recognition of three types: OX 2, OX 19, and OX K, by virtue of the Weil-Felix reaction. While these antigens are important in the diagnosis of typhus fever and other rickettsial diseases, they have little clinical bacteriologic applicability.

FEMALE GENITAL TRACT INVOLVEMENT

The *Proteus* group is part of the naturally occurring flora of the gastrointestinal tract and secondarily colonizes the genitourinary tract. Although *Proteus morganii* has been incriminated in summer diarrhea in children, it is only when the organisms leave their normal habitat in the gastrointestinal tract and are placed in a specific milieu where they do not have to compete with the predominant *Escherichia coli* and *Klebsiella* organisms

that they produce infection in man. They are present in large numbers in the gastrointestinal or vaginal flora only when some abnormality occurs which facilitates their multiplication. By and large, the *Proteus* organisms do not function as prime pathogens for man. Even though they cause genitourinary and gastrointestinal infections, they do so primarily after more drug-sensitive enteric pathogens have been eradicated. Urinary tract, wound, and neonatal infections are the predominant forms of *Proteus* infection encountered in obstetrics and gynecology.

Urinary tract infection

The indole-negative strains (i.e. *P. mirabilis*) account for 8–9% of isolates obtained from patients with asymptomatic bacteriuria in pregnancy. Their relative prevalence as isolates from cases of pyelonephritis is markedly decreased. The recovery of an indole-positive *Proteus* from a patient with urinary tract infection often reflects prior administration of antibiotic agents. Infections with urea-splitting bacteria are likely to be associated with or causally related to renal calculus formation. In rare instances, as a consequence of internal metabolic derangement resulting in a persistently alkaline pH, *Proteus* may be the initial pathogen of the female genital tract. Such an alteration of pH permits the clinical expression of an organism of a lower pathogenicity. The group does not flourish at an acid pH. Therapeutic use of this biologic property may be an important adjunct to therapy for a given patient.

Wound infection

The factors permitting replication of *Proteus* bacilli in the urinary tract are similar to those that function in local wound infection. The organism appears in large numbers in wound infections either by virtue of its ability to overgrow drug-sensitive species or because local growth conditions, such as pH, have had a selective influence on the bacterial flora at the site of infection. One of the important considerations is the fact that *Proteus*, at the site of wound sepsis, may be masking the identification of another pathogen—hence the necessity to reculture either the wound or the original specimen on specific media that inhibit swarming before a cause-and-effect relationship is attributed to the organism.

Neonatal infection

Neonatal infection due to *Proteus* organisms is rare. When it occurs, it tends to take the form of meningitis and meningoencephalitis. *Proteus* is the cause of acute neonatal meningitis in approximately 4% of reported cases. Even in adults and older children, *Proteus* meningitis is rare; it is limited to cases of severe otitis media with sinus thrombosis. *Proteus* does not frequently constitute a significant part of the maternal vaginal flora unless the patient has been exposed to extensive broadspectrum antibiotic therapy prior to vaginal delivery. Neonatal acquisition of infection is rarely associated with parturition through an infected birth canal. The neonatal umbilical vessels constitute the primary portal of infection, and the disease occurs primarily in patients requiring extensive and prolonged hospital care. Just as with the *Pseudomonas* organisms, the

presence of a large vascular channel permits the clinical expression of infection. The signs and symptoms of *Proteus* infection are those of respiratory and central nervous system involvement. The infants exhibit grunting, restlessness, pyrexia, and, in advanced cases, evidence of meningitis in the form of stiff neck. A not uncommon feature of neonatal infection is an erythematous rash, which occasionally may exhibit focal hemorrhage. At necropsy the cranial cavity has a characteristically fetid smell, the cerebral hemispheres are soft and swollen, and various degrees of intracerebral hemorrhage can be identified. Microscopic identification of necrosis within cerebral tissue can be made. The blood vessels show a series of changes ranging from bacterial vasculitis unassociated with significant inflammatory infiltrate to fibroid necrosis of the vessel. While an inflammatory reaction in the vessels may be absent despite an intensive bacterial infiltration of the wall, acute inflammatory cells are common within the meninges. The occurrence of *Proteus* meningitis and its extreme lethality in the neonate stress the necessity for compulsive care of the umbilical stump.

THERAPY

For clinical purposes the *Proteus* group can be subdivided into indole-positive and indole-negative subgroups. The justification for this distinction based on a metabolic characteristic is the divergent pattern of antibiotic sensitivity in the two groups. Indole-positive strains of *Proteus* are resistant to ampicillin and selected cephalosporins, whereas most strains of the indolenegative organisms are highly susceptible to these agents. Indole-positive strains (e.g. *P. vulgaris*) and indole-negative strains (e.g. *P. mirabilis*) are susceptible to aminoglycosides such as gentamicin. The aminoglycosides and the fluoroquinolones are currently the drugs of choice against indole-positive *Proteus* whereas ampicillin is the drug of choice for *P. mirabilis*.

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40
Staphylococci

The staphylococci are large, Gram-positive cocci which, in liquid or on solid media, aggregate in grapelike clusters. This morphologic pattern which typifies staphylococci is the consequence of random cell division in three planes. The staphylococci are covered with a carbohydrate surface slime that forms intracellular bridges linking the cocci together in this arrangement.

The organisms were first cultured *in vitro* by Louis Pasteur in the year 1880. Two years later, Ogston named this unique genus of spherical, cluster-forming microorganisms the *Staphylococcus*. By 1886, predicated on the pigment production or the lack of it, Rosenbach defined two distinct subspecies: *Staphylococcus pyogenes aureus* and *Staphylococcus pyogenes albus*. However, the criterion of pigment production, which originally separated the staphylococci into distinct genera, is now regarded as a minor criterion for identification.

STAPHYLOCOCCUS AUREUS (COAGULASE-POSITIVE)

The typical morphology of *S. aureus* is characterized by golden yellow, glistening colonies, 1–2 mm in diameter, which may be surrounded by a zone of beta-hemolysis when grown on 57% sheep blood agar. Individual strains may or may not be encapsulated. The enhanced virulence of the encapsulated strains is attributed to a polysaccharide capsular surface antigen which requires antibody adherence and coating for optimal phagocytosis. This antigen may block the coagulase reaction as well as phage attachment. Anaerobic fermentation of mannitol and production of coagulase and extracellular deoxyribonuclease (DNAse) are the principal features which distinguish *S. aureus* from *S. epidermidis*.

The staphylococci possess multiple type-specific antigens. Individual strains can be differentiated by antigen analysis using prototype-specific antisera. The antigenic complexity of *S. aureus* and the lack of common reagents restrict the usefulness of this immunologic serotyping. Phage typing is currently performed using bacteriophages (viruses that infect bacteria). This typing is based on the phage lysis of susceptible bacterial cells, and the inability to lyse resistant ones. The patterns formed by lysis, or lack thereof, by 22 phages permit the classification of *S. aureus* into four major groups. Staphylococcal isolates that differ by their reactions to two or more phages are considered different.

Staphylococcus aureus is etiologically responsible for a number of clinical entities, including wound infections, progressive synergistic bacterial gangrene, the anaerobic progression (see under Bacteroidaceae), urinary tract infection, septicemia, puerperal mastitis, and toxic shock syndrome.

Wound infections and synergistic bacterial gangrene

The coagulase-positive staphylococci, one of the important constituents of the microbiologic flora of the skin, may play an important role in wound infections. Infection may be both endogenous, arising from strains colonizing the patient's skin, upper respiratory tract, or female genital tract, and exogenous, being acquired from the environment or the microbiologic flora of another individual. The prevalence of *S. aureus* in the microbiologic flora of the skin is in contrast to its relatively low representation in the vaginal flora. When present in conjunction with an appropriate oxidation-reduction potential, *S. aureus* organisms can function as class I through III anaerobes. Its ability to replicate under both aerobic and anaerobic conditions and to synthesize bacteriocins or bacteriocin-like substances enhances the clinical recognition of this organism as a cause of wound infections while the more obligatory anaerobes, which may be concomitantly involved, often escape recognition. A foul-smelling discharge should suggest the presence of concomitant anaerobic infection, even though routine anaerobic cultures may reveal only *S. aureus*.

The clinical manifestations of wound infections are primarily local tenderness, edema, and erythema. The discharge from staphylococcal wound infections is purulent. Gram-staining readily demonstrates the presence of large, Gram-positive cocci in clusters. Unless systemic signs of infection are present, as evidenced by fever and leukocytosis, the primary mode of therapy comprises drainage, surgical debridement, and appropriate wound care. The persistence of a low-grade fever which never returns to baseline levels despite apparent adequate antimicrobial therapy should alert the physician to the possibility of an undrained wound or collar-button abscess.

Staphylococcus aureus functions as a copathogen in progressive synergistic bacterial gangrene. In this situation, microaerophilic streptococci combine with *S. aureus* to produce a progressive gangrenous cutaneous lesion. Diagnosis and therapy are discussed in the section on necrotizing wound infections.

Role in the anaerobic progression

Though rarely isolated from abscesses *per se*, *S. aureus*, like the Enterobacteriaceae, may be the trigger organism for the rupturing of a tubo-ovarian abscess. Whereas local care and debridement are the prime keys to the management of wound infections, infections in continuity with the vaginal mucosa in which *S. aureus* functions as a copathogen require eradicative antibiotic therapy.

Urinary tract infection

Staphylococcus aureus is a potential causative agent of asymptomatic bacteriuria or pyelonephritis. However, its prevalence in either category of patients is of the order of 0.1%. Therapeutically, both conditions should respond to an effective antibiotic regimen. What singles out *S. aureus* pyelonephritis for special attention is that in about 20% of the cases, renal parenchymal involvement is due to hematogenous rather than ascending infection. In these instances, the correct diagnosis is not pyelonephritis, but rather focal embolic glomerulonephritis with parenchymal extension secondary to unrecognized bacterial endocarditis or osteomyelitis (the latter is rare in women of childbearing age).

Refractory anemia, an inverted albumin-globulin (A/G) ratio, and a persistently elevated erythrocyte sedimentation rate, as well as evidence of focal embolic phenomena involving the retina or conjunctiva of the eye or appropriate cutaneous sites (petechial hemorrhages, Janeway lesions, Osler's nodes, etc.) may corroborate the diagnosis of hematogenous renal involvement. Pyelonephritis due to *S. aureus* in a drug addict should be equated with a presumptive diagnosis of bacterial endocarditis until proved otherwise. In cases of acute staphylococcal endocarditis, the infected emboli within the glomeruli may develop into multiple renal abscesses. These abscesses may coalesce to form a renal carbuncle or extend beyond the capsular confines to create a perinephric abscess. The usual presenting features of a renal or perinephric abscess are rigors, spiking fever, and flank pain. Both of these conditions require surgical intervention.

Septicemia

The most challenging problem which *S. aureus* poses for obstetricians and gynecologists is that of septicemia. Although septicemia may complicate any of the previously described disease processes, the problem is usually iatrogenic, engendered by the infection of intravenous catheters by *S. aureus*. Once the appropriate blood cultures have been obtained, all intravenous catheters should be removed and the tips cultured and Gram stained. The bacterial strains, being of nosocomial origin, tend to be resistant to penicillin. A penicillinase-resistant semisynthetic penicillin should therefore be used until antibiotic sensitivity tests sanction or contraindicate the use of a cephalosporin or penicillin G in the case of sensitive strains. The duration of therapy is critical. Despite eradication of the septicemia by appropriate antistaphylococcal therapy, death may result from late sequelae. Depending on its duration and magnitude, staphylococcal septicemia may produce severe metastatic complications. Osteomyelitis or brain abscesses may not become clinically manifest for 6–8 weeks following vascular invasion. To avert the possible metastatic complications, once staphylococcal septicemia has been documented, one is committed to a minimum of four weeks of therapy.

Catheter-associated septicemia is intermittent, in contrast to the continuous bacteremia of staphylococcal endocarditis. The diagnosis of bacterial endocarditis is inferred by demonstrating the persistence of septicemia after the removal of an infected intravenous line.

Staphylococcus aureus may function as a systemic pathogen following hypertonic saline abortion. The frequency with which *S. aureus* is isolated from the intravascular compartment in this clinical situation argues for the use of antibiotic coverage effective against *S. aureus*.

Gel diffusion or countercurrent immunoelectrophoresis (CIE) may aid in the differentiation between well-established, prolonged staphylococcal septicemia and that of recent onset. Gel diffusion tends to be markedly less sensitive than CIE, demonstrating a cross-reaction with streptococci in a significant number of instances. Countercurrent electrophoresis is more sensitive; however, there is a higher rate of false-positivity. If such sophisticated technology is available, one would first do a CIE. If a positive identification is established, then one would resort to gel diffusion for confirmation.

In rare instances, one can produce a transient septicemia as a consequence of a surgical procedure on a cutaneous staphylococcal abscess. To prevent spread either by

bloodstream dissemination or by direct local extension, antibiotic prophylaxis is recommended prior to the cutaneous drainage of furuncles on the head or neck or of large lesions with evidence of peripheral extension. Antibiotic administration should be continued for a minimum period of three days.

Puerperal mastitis

Puerperal mastitis is a disease of the post-gravid female which has its genesis in the neonate. The newborn infant becomes colonized within the nursery by a nosocomial penicillin-resistant *Staphylococcus*. Approximately 50–75% of nursing personnel are probable *Staphylococcus* carriers and a permanent source of penicillin-resistant organisms within the hospital environment. The infant becomes the prime disseminator of the staphylococci to the mother. Maternal infection is almost invariably due to a hospital-acquired and not an endogenous strain, unless the mother had a staphylococcal cutaneous infection which antedated her hospital admission.

The determinants of disease, as opposed to colonization, are difficult to discern. At least one of these appears to be the strain virulence of the organisms. A high rate of breast infection occurs among nursing mothers when there is a concomitant epidemic of overt *S. aureus* infection in the newborn nursery. Even then, there is far from a one-to-one correlation between colonization of a neonate with a virulent strain of *S. aureus* and subsequent maternal puerperal mastitis. Given the colonization of newborn infants with an epidemic strain, a few mothers will develop puerperal mastitis, but the majority will not.

The disease occurs most commonly between the 11th and 30th day postpartum, the greatest number of cases being identified in the second to third week. Infection is usually a unilateral phenomenon. With progressive engorgement of the ducts, the breast becomes engorged, resulting in a discrete tender mass. Cutaneous erythema develops locally. With progression of the disease the patient may experience chills, fever, headaches, and malaise.

The conversion of mastitis to abscess occurs extremely rapidly. If specific therapy is not instituted within the first 24–36 hours, abscess is the usual sequela of puerperal mastitis, particularly when due primarily to *S. aureus*. Antibiotic therapy, to be effective, must be administered within the first 24 hours. The critical factor is the time of administration, namely, prior to the establishment of an irreversible process, rather than the choice of antibiotics *per se*. Both cephalothin and erythromycin are effective in this clinical setting.

Methicillin-resistant Staphylococcus aureus

Methicillin-resistant *Staphylococcus aureus* (MRSA) was initially detected in Europe in the 1960s, soon after the introduction of methicillin. Naturally-resistant strains were isolated in some countries before the use of methicillin or related agents. These strains spread initially from one or more ancestral genetic clones in natural populations of *S. aureus* by horizontal transfer and recombination. These original strains then increased in numbers and diversity in hospitals as a result of selection by exposure to antibiotics and

by cross-infection. The main mode of spread is person-to-person within a unit or hospital and subsequently to other hospitals.

To date, MRSA has not been a major problem in Obstetrics and Gynecology, only because of patient predisposition to disease conversion. Risk factors for MRSA bacteremia include: a higher frequency of severe underlying disease, poorer underlying prognosis, prior antibiotic therapy, prolonged hospitalization, intravascular catheterization, and intensive care unit location. Risk factors for developing MRSA postoperative wound infections include: prior antimicrobial therapy, prolonged hospitalization and severity of underlying disease. Few data are available to identify specific risk factors for colonization or infection of burn wounds by MRSA. Rapid detection of MRSA prompt implementation of barrier precautions and prospective surveillance are essential components of a successful control program. Eradicating nasal carriage of MRSA among patients and personnel can be useful during epidemics.

Resistance to methicillin is due to chromosomally mediated alteration in the penicillin-binding proteins. Low affinity penicillin-binding protein PBP-2a encoded by mecA is closely related to methicillin resistance in staphylococci. The management and therapy of MRSA is included in the chapter on Nosocomial infections (Chapter 72).

Staphylococcal bacteremia associated with infected intravenous lines

Resistance by *S. aureus* is mediated primarily through two mechanisms:

(1) the elaboration of penicillinases; and
(2) mutational changes in the penicillin-binding proteins.

Production of penicillinase negates the microbiological efficacy of the first four generations of the penicillins and necessitates the use of a penicillinase-resistant semisynthetic analogue or penicillinase-resistant second- or third-generation cephalosporin. A change in the penicillin-binding proteins selects for broad cross-resistance and necessitates the use of vancomycin. Currently, the staphylococci are classified as members of the family Micrococcaceae. The staphylococci have three clinically important species: *S. aureus*, *S. epidermidis*, and *S. saprophyticus*. The teichoic acid antibody (TAA) assay measures the presence or absence of antibodies to the teichoic acid moiety in the wall of *S. aureus*. The major role of this assay is not only to diagnose *S. aureus* infection, but to determine how long to treat bacteremic patients. Patients with *S. aureus* metastatic abscesses will usually develop TAA 2 to 3 weeks after the onset of the bacteremia (Figure 40.1). A titer of greater or equal to 1:2 favors the presence of a deep-seated staphylococcal infection. The predictive value of a negative assay in someone who has experienced an episode of *S. aureus* bacteremia is high. The test is useful in ruling out metastatic disease. If TAA antibodies are absent and serial tests remain negative, the prognosis is good. Therapy can be limited to four as opposed to six weeks. The interim between bacteremia and secondary sequelae is usually about two to three weeks.

Once having attained vascular access, *S. aureus* has the potential for the induction of secondary metastatic disease involving primarily the lungs, heart valves, brain, bone, and kidneys. The incidence of infectious endocarditis following bacteremia from an infected

intravenous site ranges from 3 to 38%. Endocarditis is associated with high morbidity and moderate mortality.

The following is the protocol advocated for the evaluation of patients with documented bacteremia associated with infected intravenous lines. The following protocol assumes that one is dealing with an individual with intact host defense mechanisms, and with no evidence of established metastatic staphylococcal disease.

(1) Remove infected intravenous site.
(2) Do a careful physical examination. Look for established disease, i.e. infectious endocarditis.

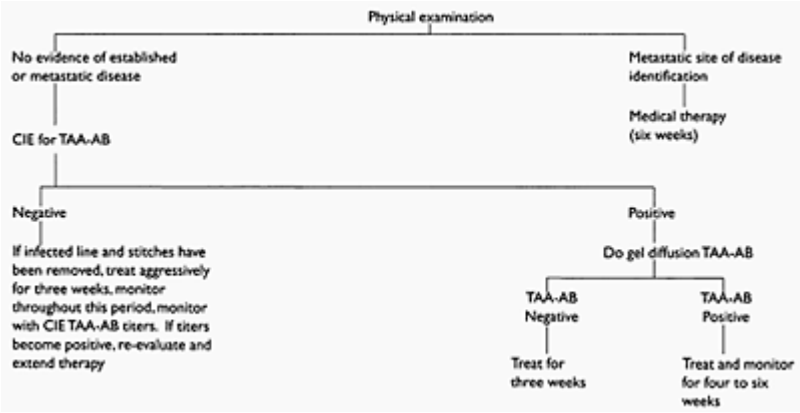

Figure 40.1 Protocol to determine the presence of metastatic staphylococcal infection following documented bacteremia (CIE, countercurrent immunoelectrophoresis; TAA-AB, teichoic acid antibody)

(3) Place patient on oxycillin.
(4) Obtain antibody titers to TAA using CIE. If TAA antibodies are to appear, they usually do so 2–3 weeks after the onset of disease. If TAA antibodies are already present, do quantitative measurements using gel diffusion. A titer greater than or equal to 1:2 favors the presence of deep-seated staphylococcal infection. One way to rule out aggressive metastatic disease is to obtain echocardiography, bone scans, and urine cultures. If TAA antibodies are absent and serial tests remain negative, the prognosis is good. Therapy can be limited to four as opposed to six weeks.

STAPHYLOCOCCUS EPIDERMIDIS

Staphylococcus aureus alone has the capacity to produce coagulase. Most laboratories label all coagulase-negative isolates as *'S. epidermidis'* which results in the failure to differentiate *S. epidermidis* isolates from *S. saprophyticus*. *S. saprophyticus* is a significant cause of urinary tract infection in otherwise healthy young women who have no demonstrable abnormalities of the urinary tract. Unlike *S. epidermidis, S. saprophyticus* can function as a primary pathogen. Both coagulase-negative staphylococci are not only a cause of urinary tract infection, but potential participants in the anaerobic progression.

Urinary tract infections

Coagulase-negative staphylococci are second only to the Enterobacteriaceae as a cause of significant urinary tract infection in young women of childbearing age with no renal abnormality. The fact that they are common inhabitants of the urethra has contributed to their presence in urine being regarded with skepticism. It should be stressed that coagulase-negative staphylococci have been isolated from urine obtained by suprapubic aspiration and by culture of renal biopsies. They are a significant cause of both upper and lower tract disease.

The wide variation in the reported incidence of Gram-positive cocci in urinary tract infections is probably influenced by two important variables. If the bacteriologist does not accept coagulase-negative staphylococci as urinary tract pathogens, an isolate may be ignored. Also, the total reliance on McConkey's medium for urinary tract bacteriology is limited by its inability to support the growth of Gram-positive cocci. Five percent sheep blood agar plates should be used in parallel to McConkey's medium. A general rule of thumb to be used by the practitioner is that a coagulase-negative staphylococcus which is novobiocin-resistant and is obtained from a young, healthy, ambulatory woman equates with *S. saprophyticus*, whereas urinary tract infection acquired within the hospital setting in an older patient usually equates with *S. epidermidis*. Although suspected on clinical grounds by the demonstration of more than 15 Gram-positive cocci per high-power field in urinary sediment, definitive diagnosis of staphylococcal infection emanates from the microbacteriology laboratory.

Septicemia

Coagulase-negative staphylococci are normal constituents of skin and most mucous membranes. As a consequence, they are common contaminants in blood culture specimens obtained across intact cutaneous barriers. Only in recent years has there been clear perception of coagulase-negative staphylococci that can function as bona fide pathogens. They have become the most common organisms isolated from infectious prosthetic heart valves, cerebrospinal fluid shunts, peritoneal dialysis catheters, and indwelling intravenous catheters. In the presence of a foreign body, the staphylococci can be formidable pathogens.

For the obstetrician/gynecologist the principal area of concern has been the Newborn Intensive Care Nursery. The technological advances necessary for the survival of low-birthweight infants have facilitated the emergence of coagulase-negative staphylococci as major pathogens in this setting. The infants with coagulase-negative staphylococcal bacteremia manifest with increased episodes of apnea and bradycardia, feeding intolerance, lethargy, irritability, temperature instability, abdominal distention, gastrointestinal disturbance, hypotension or poor perfusion, pallor and/or cyanosis, and tachycardia. Laboratory findings include a shift in the polymorphonuclear leukocyte count resulting in leukocytosis or leukopenia, increase in immature granulocyte fraction. metabolic acidosis and hypoglycemia. The clinical management of coagulase-negative bacteremia includes antibiotic therapy in combination with removal of the foreign body. Unlike the community-acquired isolates causing disease, the nosocomially acquired strains which cause septicemia are beta-lactam resistant.

Wound infections and anaerobic progression

Regardless of the nature of the specimen, whether an exudate from an infected wound or blood from a patient with septicemia, the presence of coagulasenegative staphylococci is too frequently dismissed as being due to contamination or as being of little significance. It is estimated that 4–5% of wounds have coagulase-negative staphylococci as a significant component. The prime function of the organism, by altering the local microbiologic environment, is to render it more conducive to anaerobic replication. *Staphylococcus epidermidis* may be present as a constituent of polymicrobial bacteremia and will undergo selective replacement by more anaerobic organisms. While it is rare for this organism to function as a virulent pathogen in systemic infection, under appropriate conditions it may be an effective pathogen for a damaged endocardium.

Neonatal scalp abscesses

Staphylococcus epidermidis is a frequent isolate from neonatal scalp abscesses. In the series reported by Plavidal and Werch, *S. epidermidis* accounted for 11 of the 19 positive cultures. In three of these abscesses, it was found with one or more other bacteria. In the majority of instances there was a good correlation between Gram stains and culture data. In one of the two cases reported by Overturf and Baalfour, the organism was the apparent cause of osteomyelitis, which was seen as a direct sequel of scalp abscess at the site of previous fetal monitoring.

STAPHYLOCOCCUS SAPROPHYTICUS

In 1963, Baird-Parker developed a scheme which divided the Gram-positive, catalase-positive, coagulase-negative cocci into staphylococci and micrococci and then subdivided them further into subgroups and biotypes. What was termed *Micrococcus* subgroup 3 is now called *S. saprophyticus*. Pragmatically, separation of other staphylococci from *S. saprophyticus* is achieved by their different sensitivity to novobiocin; *S. saprophyticus* is generally resistant, while *S. epidermidis* is usually sensitive.

Staphylococcus saprophyticus causes urinary tract infections more frequently in women without previous symptoms than among those with a history of recurrent urinary tract infection. *S. epidermidis* usually produces asymptomatic bacteruria, *S. saprophyticus* is usually associated with clinically overt disease. The magnitude of pyuria is comparable to that seen with other urinary tract pathogens.

The organism gains access to the female urinary tract from a fecal reservoir. Its prevalence in a given population varies significantly. A possible explanation is inferred from a Swedish study in which *S. saprophyticus* was recovered from a variety of food which may function as the vehicle from gastrointestinal tract colonization. When recolonization occurs, it tends to be due to a different strain of *S. saprophyticus*.

THERAPY FOR STAPHYLOCOCCAL DISEASE

Staphylococcus aureus

Therapy is predicated on whether one is dealing with monoetiologic disease such as that seen with *S. aureus* or urinary tract infection due to the coagulase-negative staphylococci or whether the organism is part of a polymicrobial infection. In dealing with a single microbe, the selection of an antibiotic is predicated on the drug of choice concept; for *S. aureus*, it must be presumed that the isolate is a penicillinase producer. At present, more than 90% of all isolates, whether nosocomial or community-acquired, are resistant to penicillin. Therefore, no patient suspected of having an infection with *S. aureus* should be started on a penicillinase-susceptible penicillin. Most staphylococci are susceptible to nafcillin and oxacillin. Usual doses of nafcillin and oxacillin are in the range of 6 to 12 g daily, and patients with endocarditis should receive between 9 and 12 g daily. In the penicillin-allergic individual, the cephalosporins can be used in the absence of a history of an anaphylactic type of penicillin hypersensitivity; however, the most effective alternative continues to be vancomycin. Vancomycin is used in a dose of 2 to 4 g per day parenterally and should be equal to the penicillins and cephalosporins in terms of therapeutic outcome. In dealing with staphylococcal septicemia, it is recommended that initial therapy involves one of the betalactamase resistant penicillins, e.g. nafcillin or oxacillin. Continued antimicrobial therapy is selected for by *in vitro* sensitivities. If the strain of *S. aureus* is sensitive to penicillin and methicillin, therapy is switched to penicillin G. If the strain is resistant to penicillin, but susceptible to methicillin, initial therapy is continued. If the strain is resistant to both antibiotics, the patient is switched to vancomycin.

Vancomycin hydrochloride is the treatment choice for empiric treatment of both coagulase-negative staphylococci infection and of those infections involving methacillin-resistant coagulase-positive staphylococci. The fluoroquinolones may be effective against the mild to moderate infection due to methacillin-resistant staphylococci. Imipenem (a carbapenem) should probably not be used despite *in vitro* sensitivity. When vancomycin resistance is identified, a fallback drug combination which may be effective is the coupling of sulfa-methoxazole-trimethoprim and rifampin.

Coagulase-negative staphylococci

Along with the increased incidence of coagulase-negative staphylococci infections, a marked increase in antimicrobial resistance has been observed. Approximately 90% of clinically encountered strains produce beta-lactamase.

Another mechanism of resistance to beta-lactam antibiotics is the production of altered penicillin binding proteins with low affinity for beta-lactam antibiotics. The detection of the methicillin-resistant phenotype can be difficult due to heterotypic expression. From 1980 to 1989 the incidence of methicillin-resistant coagulase-negative staphylococci rose from 20% to 60%. Most methicillin-resistant isolates are also resistant to other multiple classes of antibiotics.

For the coagulase-negative staphylococci, it is indispensable to determine disc sensitivities or minimum inhibitory concentrations (MIC) for all coagulase-negative septicemic isolates. Due to the high prevalence of methacillin-resistant isolates, the use of vancomycin is advocated. Being methicillin-resistant equates with resistance to all beta-lactam antibiotics regardless of *in vitro* data to the contrary, aminoglycosides and most macrolides and tetracyclines.

The only available agents with consistent activity against multi-resistant coagulase-negative staphylococci are vancomycin and rifampin. Some strains remain susceptible to aminoglycosides, trimethoprim-sulfamethoxazole, clindamycin, minocycline or fluoroquinolones, and therapy should be guided by susceptibility testing. Rifampin should never be used alone in the treatment of coagulase-negative stapylococci infection as resistant isolates rapidly emerge.

Optimum therapy of nosocomial coagulase-negative staphylococci requires the combination of two or three agents. Such agents as gentamicin, trimethoprim-sulfamethoxazole, clindamycin, minocycline, a fluoroquinolone, or various investigational drugs in combination with vancomycin and/or rifampin against susceptible isolates appear to be viable therapeutic options.

Staphylococcus saprophyticus

S. saprophyticus readily responds to most urinary tract antimicrobials, except for nalidixic acid.

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Methicillin-resistant *Staphylococcus aureus*

(see Methicillin-resistant *Staphylococcus aureus* within Chapter 72, Nosocomial infection)

41
Group B streptococci

The group B beta-hemolytic streptococcus *(Streptococcus agalactiae)* is a Gram-positive coccus which grows in chains *in vitro* and *in vivo*. On appropriate media the colonies appear as smooth, shiny white mounds, about 1–1.5 mm in diameter, with a narrow zone of beta-hemolysis. The group B streptococcus (GBS) lacks the M protein that is characteristic of the group A organisms; consequently, its virulence and pathogenicity for humans differ markedly from those of *Streptococcus pyogenes*.

Originally isolated from cows with mastitis, the GBS was regarded as a bovine organism and not as a prime pathogen for man; hence the original name *Streptococcus mastitidis*. Once Lancefield had provided a basis for classification that was independent of the type of hemolysis and metabolism of specific carbohydrate substrates, GBS were found in the human nasopharynx and upper respiratory tract, as well as in the normal flora of the female genital tract. Occasionally, the organisms may also be found on the skin.

On the basis of divergent carbohydrate antigenicity, the GBS can be divided into nine serotypes: Ia, Ib/c, Ia/c, II, IIc, III, IIIc, IV and V. Lancefield originally described two cell wall polysaccharides:

(1) the group B-specific immunogen common to all strains of the species; and
(2) that of type-specific immunity which allowed subsequent subdivision into four serotypes: Ia, Ib, II, and III.

The major antigenic determinant for the GBS is L-rhamnose. Type I strains have three antigenically distinct polysaccharide constituents designated Ia, Ib/c and Ia/c. Specific anticarbohydrate antibodies confer passive protection to mice challenged with homologous streptococci. The classic virulence seen with group A streptococci is not found among GBS organisms. GBS function as opportunistic organisms whose pathogenicity is usually linked to some alteration of strain virulence.

EPIDEMIOLOGY

The GBS are normal constituents of the vaginal flora. The principal reservoir is the gastrointestinal tract. When single sites of prevalence are evaluated, the fecal colonization rate exceeds both the cervical-vaginal and the throat colonization rates. Sahradnicky reported a family study with the index case being an infant who died of group B sepsis. Both mother (vagina and cervix) and father (urethra) carried the same strain that was cultured from the child at autopsy. Despite aggressive antimicrobial therapy, the organism showed prolonged persistence in the gastrointestinal tracts of the parents and was responsible for intermittent recolonization of the genitalia.

Between 14% and 25% of pregnant women may be continually, intermittently, or transiently colonized. The overall incidence of vaginal colonization is relatively consistent. Preliminary data suggest that approximately one-third of bacterially colonized women are positive throughout pregnancy. Another one-third have transient vaginal colonization, and the remaining gravidas have spontaneous clearance of the GBS at the time of delivery. The pattern of colonization is influenced by a number of factors. Women with two or more previous pregnancies tend to be more frequently colonized than primigravidas or secundigravida. Data emanating from the Vaginal Infections and Prematurity Study Group demonstrated that GBS colonization was more common among older women and women with multiple sexual partners.

The major reservoir of the GBS is the gastrointestinal tract. Their preferential growth in an aerobic environment leads to their potential, if not probable, dissemination by coitus. The bacteria can be cultured from the urethra of 50% of sexual consorts of vaginally colonized women. The rate of recovery of GBS is significantly lower in women with no history of sexual intercourse than in women with a history of sexual intercourse with one or more sexual partners. The incidence of bacterial isolation is increased among women of lower socioeconomic groups.

SPECTRUM OF DISEASE

Urinary tract infections

Urinary tract infections due to streptococci are caused almost exclusively by groups B and D. Of 205 streptococcal group B isolates from extrarespiratory infections, 32% were from urine. Feingold *et al.* noted a surprisingly high incidence of urinary tract infections due to GBS. They pointed out that the frequency of group B infection is probably underestimated. Even though pyelonephritis secondary to GBS is a definite entity, it accounts for only a very small percentage of the cases of pyelonephritis observed during gestation. Infection responds to ampicillin.

Asymptomatic group B bacteriuria and pregnancy

The identification of GBS as a cause of asymptomatic bacteriuria in pregnancy appears to select for a higher probability of maternal and/or neonatal infection. Persson *et al.* studied women with asymptomatic bacteriuria comparing void urine specimens with greater than or equal to 10^5 colony-forming units (cfu)/ml and the occurrence of bacteria in the urinary bladder detected by bladder puncture. The only infant who contracted early onset septicemia was born to a patient with growth of GBS type III in voided urine. During pregnancy the mother repeatedly voided specimens with greater than or equal to 10^5 cfu/ml. She was not treated with antibiotics.

Moller *et al.* identified 68 women out of a group of 2745 consecutive gravidas sampled who had asymptomatic bacteriuria (ABU) due to GBS. The incidence of primary rupture of the membranes and premature delivery was 35% and 20%, respectively, in contrast to 15% and 8.5% in gravidas without GBS ABU. The five cases of GBS neonatal sepsis (four of which died) occurred in the progeny of women with positive urine

cultures. Greater than 10^5 cfu per ml of urine appears to be of more predictive value than quantitative studies of vaginal prevalence.

These data substantiate an earlier study by Wood and Dillon in which they prospectively followed forty-six patients with bacteriuria. The only adverse fetal outcome following any bacteria was observed with asymptomatic GBS bacteriuria. Two pregnancies ended in intrauterine fetal death and one neonate developed GBS sepsis. They concluded that screening for GBS bacteriuria at or near delivery may be more meaningful than other GBS surveillance culture studies.

Genital tract infections

While they are endogenous bacteria for the female genital tract under selected conditions, the GBS can function as formidable adversaries. They are the second most common cause of septicemia in postpartum women, a fact largely overshadowed by their potentially devastating effect on the neonate. As causes of monoetiologic disease, they may produce chorioamnionitis, postpartum endometritis, and maternal septicemia. They can function in polymicrobial postpartum endometritis as a constituent of the anaerobic progression.

Sutton *et al.* pointed out that under selected conditions, the group B as well as the group A beta-hemolytic streptococci can produce necrotizing fasciitis. Acute endocarditis and pneumonitis have been observed following septic abortion or other forms of puerperal infection resulting in sustained septicemia. Sexton *et al.* reported two fatal cases of acute endocarditis involving the aortic valve which occurred in one woman after a normal pregnancy and delivery and in the second woman after a second trimester abortion. Both women were thought to have normal heart valves before the onset of their infection. Both of these women with acute aortic valvulitis due to the GBS went on to develop annular abscesses and then died.

The ability of the GBS to produce disease in gynecologic-oncologic patients is linked to certain predisposing factors: diabetes mellitus, carcinomatosis, or some form of debilitating chronic disease. The most frequent manifestation of disease in this patient population is an acute cellulitis.

Perinatal colonization

Given a mother whose bacterial flora contains the GBS, what is the probability of early bacterial colonization of the offspring by either ascending infection from the vagina or delivery through an infected birth canal? At 36 hours of age, colonization of surface sites or mucous membranes among all infants has been detected in 26–37% of neonates. Approximately one-third of the isolates are type Ia, Ib/c, or Ia/c; one-third are type II or IIc; and one third are type III. The almost complete concordance of identical serotypes among isolates from mothers and their progeny partially substantiates the hypothesis that early-onset syndrome is the consequence of vertical bacterial transmission from mother to neonate. The overall attack rate for the early-onset type of disease has varied from 3.0 to 4.2 per 1000 live births. The attack rate for colonized newborns is approximately 1 per 1000 live births. The mortality rate is of the order of 1–2 per 1000 live births. Attack

rates for late-onset infection have been estimated to be between 1.5 and 2.0 per 1000 live births (Table 41.1).

Factors influencing the neonatal attack rate include:

(1) smallness-for-dates or prematurity;
(2) premature rupture of the fetal membranes;
(3) lack of passive immunity derived from the mother; and
(4) the ability of a given isolate of GBS to adhere to cell surfaces.

Infants born to culture-negative women may acquire the bacterium from the hospital environment. In one nursery studied, infant colonization has been reported to increase from 20–25% during the first 24 hours of life to 50–65% at the time of discharge. It is presumed that the mode of nosocomial transmission is the crosscolonization of the infants as a consequence of contact with nursery personnel. When prospectively followed, those infants who became thus colonized have to date not developed late-onset GBS disease.

The problem of chronic carriage and its potential for an adverse perinatal impact in subsequent pregnancy has been studied by Dykes *et al.* They prospectively monitored for up to 38 months eight women who had given birth to infants with early-onset or intrauterine infections caused by GBS. Seven of the eight exhibited persistent carriage of the same serotype in contrast to only 34 of 88 GBS carriers who had given birth to healthy infants. Examples of recurrent early-onset septicemia exist in the literature.

Neonatal septicemia and meningitis

The major problem that the GBS cause for the disciplines of obstetrics and pediatrics is that they have been the most common cause of neonatal septicemia in the United States for the past 10 years. Two factors select for a statistically significant increase in the anticipated attack rate of early-onset disease by the GBS:

(1) ability to establish urinary tract colonization (asymptomic bacteriuria); and
(2) ability to establish high density replication with vaginal and rectal bacterial flora.

EARLY-ONSET VERSUS LATE-ONSET NEONATAL DISEASE

The GBS produce two patterns of neonatal disease which are predicated on the time of onset (Table 41.1).

Early-onset disease

Early-onset neonatal infection caused by streptococci of Lancefield group B has an incidence of approximately 2–3 cases per 1000 live births. Early-onset septicemia is defined as disease whose onset occurs when infants are less than five days old. It is characteristically associated with maternal factors (i.e. premature rupture of the membranes (PROM) cesarean section, etc.). Bacterial access to the neonate is primarily a consequence of intrapartum transmission resulting from delivery

Table 41.1 Clinical comparison of early-onset and late-onset neonatal disease due to group B streptococci

Property syndrome	*Early-onset syndrome*	*Late-onset syndrome*
Definition	The onset of clinical disease in the first 5 days of life (75% identified in the first 24 hours)	The onset of clinical disease after the 10th day of life
Predominant site of involvement	Lungs	Central nervous system
Clinical presentation	Pulmonary—apnea, tachypnea and low peak ventilatory pressure on mechanical ventilation	Meningeal—stiff neck, clouding of sensorium, failure to feed, bulging fontanelles
Serotypes	Proportionately distributed between types Ia-c, II, III; serotype matches that of the mother's vaginal flora	Greater than 90% due to type III; a significant number of infants culture negative at birth
Gestational or maternal factors	Small-for-dates or premature infant, premature rupture of membranes, postpartum maternal endometritis, maternal fever	Prematurity; nosocomial acquisition of type III in the newborn nursery
Morbidity/mortality	Slightly in excess of 50% mortality; sequelae*	Death less frequent (12–18%); neurologic
Attack rate	3.0–4.2/1000 live births	0.5–1.0/1000 live births

*Sequelae include retarded speech and language development, transient hemiparesis, retarded psychomotor development,seizure disorders, and hydrocephalus. (Monif GRG. *Infect Dis Letters Obstet Gynecol* 1975; 1:25)

through an infected birth canal. Once labor has occurred, the GBS may gain access to the amniotic fluid despite the presence of intact fetal membranes. Early-onset disease presents with predominantly pulmonary findings. The clinical manifestations include apnea and tachypnea. The prime differential diagnosis is that of early-onset versus respiratory distress syndrome. There are only a few diagnostic modalities which may be of assistance in differentiating the two, the principal one being roentgenography. A small percentage of patients present with shock. Mortality has been significantly reduced from 15–20% to 2–5% with aggressive therapy and early intervention. If serotyping is done, 18–28% of the cases are found to be due to type Ia, Ib/c, or Ia/c; 35–44% to type II or IIc; and 33–37% to type III. The timing of early-onset disease is such that the bulk of disease develops in the immediate neonatal period. About 52% of the cases will be identified in the first 6 hours and almost 75% of the cases will be identified in the first 24 hours.

Early-onset disease is primarily a complication of immature and premature neonates. The major risk factors for the induction of disease are:

(1) small-for-dates or premature infants;
(2) pulmonary immaturity; and

(3) PROM greater than 12 hours.

Where one or more risk factors are present, the incidence of disease is 7.6/1000 live births. If risk factors are absent the incidence of disease is 0.6/1000 live births. The attack rate for newborns whose gestation was greater than 37 weeks and whose membranes were ruptured less than 12 hours is approximately 1/1000 live births; however, if intrapartum fever occurs, the attack rate jumps to 130/1000 live births.

Late-onset disease

Late-onset syndrome is defined as disease which occurs after the tenth day of life. Maternal predisposing factors are infrequently present. Rather than presenting as a septicemia, the prime manifestation is a pure meningitis with or without concomitant septicemia. Whereas the serotype of the organisms responsible for early-onset disease parallels that found in the population, more than 90% of the cases of late-onset syndrome are due to type III bacteria. It is conjectured that in the majority of these cases there was a lack of passively acquired immunity of maternal derivation. It is probable that with late-onset disease a combination of host factors and nosocomial influences select for disease. While death is a less frequent outcome, the incidence of neurologic sequelae observed with the late-onset type varies from 22% to 50%.

Clinical management

The drug of choice in the treatment of early- or late-onset disease is ampicillin, in a dosage of 100–150 mg/kg body weight per day administered IV. The reason for the selection of ampicillin over penicillin is the bioavailability of the antibiotic, in terms of its ability to traverse the blood-brain barrier. Two to 18% of infants with early-onset syndrome will die. The critical factor in determining outcome is the point at which drug therapy is initiated. If more than 4 hours have elapsed between the onset of disease and the institution of therapy, the probability of a good outcome is markedly diminished.

PREVENTION

For the infected neonate, however, the answer does not lie with therapy but rather with prevention. In this vein, three divergent tracks have been developed to negate neonatal mortality and morbidity due to the GBS:

(1) maternal vaccination;
(2) eradication of the maternal carrier state by systemic antibiotic administration; and
(3) prophylactic antibiotics for the neonate.

Maternal vaccination

Current attempts at vaccine development may be a valid approach for late-onset syndrome. But for early-onset disease, it probably will not be effective in terms of either

efficacy or cost analysis, because five serotypes exist with early-onset disease as opposed to a single dominant serotype with the late-onset syndrome.

Significance of GBS colonization

The administration of antibiotic to the maternal carrier presumes that colonization *per se* is a risk factor. Attempts at eradication of the maternal carrier state are complicated by the reintroduction of bacteria from the gastrointestinal reservoir or by the sexual consort. It has been shown that the maternal carrier state can be eradicated; however, it requires that antibiotics be administered at the time of parturition. Close analysis indicates that this approach is not a cost-effective one, and the risk of anaphylaxis to penicillin or its derivative products is real. There is not a one-to-one correlation between the maternal carrier and the ensuing neonatal disease. Approximately 15–25% of pregnant women will harbor the organism, yet the attack rate in their offspring is somewhere of the order of 3–4 per 1000 deliveries.

Bobitt *et al.* evaluated 718 prenatal patients with several cultures. Complications occurring more frequently in prenatal GBS carriers were:

(1) collective morbidity;
(2) low birthweight infant; and
(3) PROM associated with low birthweight.

Maternal pelvic infection and neonatal sepsis were increased in colonized women at delivery. Maternal colonization did not predict ensuing morbidity. The predictive value of a positive prenatal culture did not exceed 8% for any of the complications. Dillon *et al.* have shown that the degree of neonatal colonization does influence the attack rate. Infants with three or four heavily colonized sites have an attack rate of 50/1000 live births. Those who were lightly colonized need approximately one-tenth of this rate.

McDonald *et al.* prospectively studied vaginal swabs from 692 women at approximately 24 weeks' gestation. GBS were detected in 91 (13.2%) women. The rate of preterm labor (PTL) was significantly higher in GBS-positive women than in GBS-negative women (18.7% versus 5.5%). This association remained significant even when patients with other recognized factors predisposing to PTL were excluded. The rate of PROM was also significantly higher in GBS-positive women (9.9% versus 2.7%) and also remained significantly higher when patients with other recognized risk factors were excluded. Pregnant women who are vaginal carriers of GBS have a significantly increased risk of PROM and PTL.

Newton and Clark noted that when they compared gravidas with and without GBS, GBS-positive patients had earlier rupture of membranes (30.7 versus 31.6 weeks) and shorter latent periods (76.8 versus 138.5 hours). Not surprisingly, chorioamnionitis and endometritis were more common in GBS-colonized gravidas.

Matorras *et al.* demonstrated that when one intrapartum vaginal culture obtained at delivery was positive, GBS could be isolated from amniotic fluid two hours after rupture of the membranes in 81% of cases. The newborns of intrapartum maternal carriers who delivered vaginally were colonized in 69.2% of cases while only 5.6% of newborns with negative cultures during delivery become colonized by GBS. In a subsequent study, the same investigators analyzed the impact of antibiotic therapy at the time of delivery.

Patients who were found to be carriers received ampicillin during delivery (500 mg i.v.) and patients without received no chemoprophylaxis. Compared with the non-carriers, the carrier patients without prophylaxis had a significant increase in the mild puerperal infective morbidity (10.6% vs. 25%). Puerperal infective morbidity in the carriers was lower than in those without prophylaxis and very similar to that of non-carrier women.

A relationship between heavy colonization and infection was initially suggested by the observations of Eickhoff and colleagues. They isolated 'pure' cultures of GBS from the genital tract in 19 of 20 patients who were cultured because of suspected infection. In their study the growth of either pure or predominant GBS in the vaginal cultures was similarly achieved from three of four mothers with chorioamnionitis. Of the 42 cultures taken from the genital tracts of infected females, Finn and Holden demonstrated a pure growth of GBS in 21 instances. Bobitt *et al.* showed heavy growth of GBS in six of seven cultures from mothers whose infants had documented early-onset septicemia. The dominance of GBS in the maternal vaginal flora may be an important if not critical factor in the ensuing infectious morbidity for the mother and her progeny. The incidence of disease is 50/1000 live births when observations are restricted to heavily colonized gravidas.

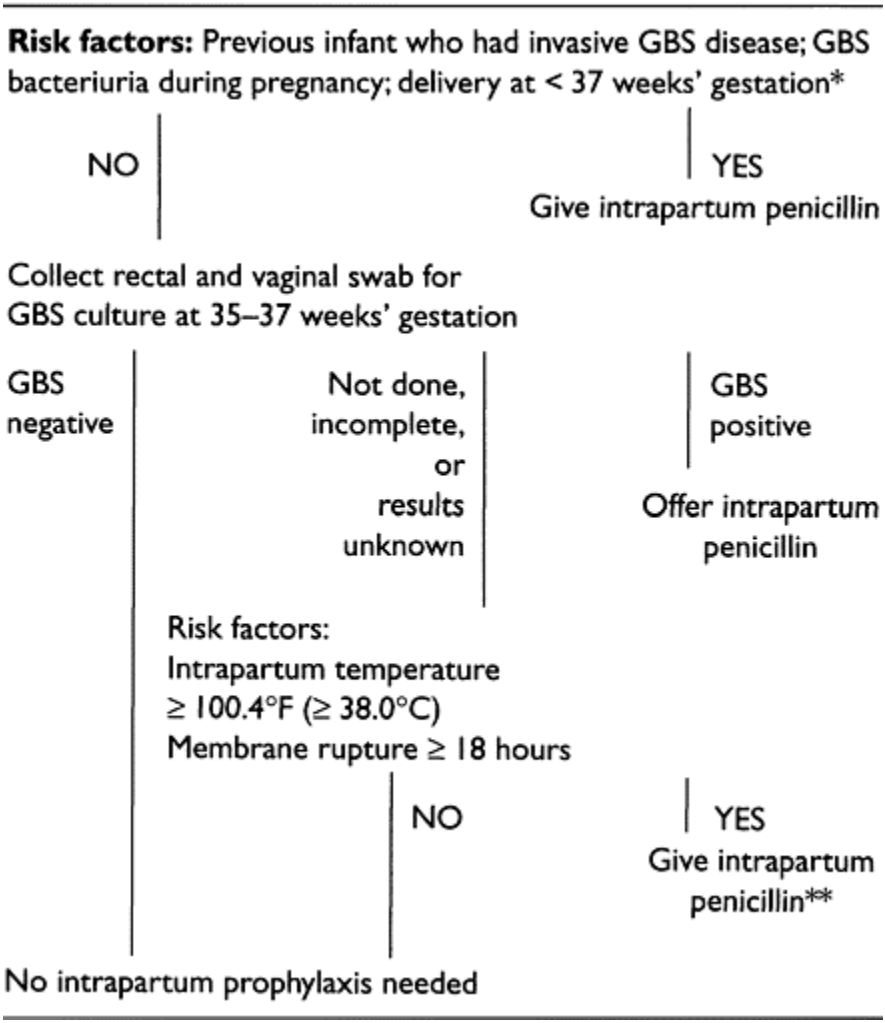
Gravidas with GBS aerobic dominance of the vaginal flora, with a preterm baby, prolonged rupture of the fetal membranes greater or equal to 18 hours or maternal intra- or postpartum infection have a greater probability of delivering a neonate who will develop GBS disease. When one of these factors are present, the risk of early-onset disease is 7.6/1000 live births. When none of these factors are present, the incidence of disease is 0.6/1000 live births.

Prophylactic antibiotics

In 1996, the Centers for Disease Control (CDC), American College of Obstetricans and Gynecologists and the Academy of Pediatrics introduced two divergent approaches for the prevention of perinatal group B streptococcal disease. The first of these, was predicated on prenatal maternal screening for GBS colonization at 35–37 weeks gestation and offering intrapartum chemoprophylaxis (Table 41.2). This approach was subsequently modified to include gravidas with GBS bacteriuria and women who had previously given birth to a GBS infected neonate. The second approach was contingent on the identification of one or more risk factors which included preterm deliveries, preterm or prolonged rupture of the fetal membranes, intrapartum fever, prior GBS neonatal disease, and GBS bacteriuria. Both approaches were initially recommended as equally acceptable.

Both approaches have been successful in altering GBS neonatal and maternal morbidity and mortality. Neither has completely eliminate the occurrence of GBS neonatal disease. The principal short-coming of a risk-based approach was the fact that 20% of GBS neonatal disease occurred in women without demonstrable risk factors. With the bacteriological screening approach for maternal GBS, the problems inherent in culturing on

Table 41.2 CDC algorithms for prevention of early onset group B streprococcus (GBS) disease in neonates using prenatal screening at 35–37 weeks



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*If membranes ruptured at <37 weeks' gestation, and the mother has not begun labor, collect group B streptococcal culture and either (a) administer antibiotics only when positive cultures are available, or (b) administer antibiotics if risk factor develops. No prophylaxis is needed if culture obtained at 35–37 weeks' gestation was negative.

**Broader spectrum antibiotics may be considered at the physician's discretion, based on clinical indications.

appropriate media, number of sites need to exclude GBS, and the ultimate site/technique for obtaining the screening culture assured less than 85% GBS detection.

Schrag *et al.* did a multi-state retrospective cohort study involving 5144 births in which they compared the efficacy of the two officially recommended approaches. In the screened group 18% of all gravidas with GBS did not present with an identifiable maternal risk-factor. These investigators found that the risk of early-onset GBS disease was significantly lower among infants of screened women than among the infants in the risk-based group by approximately 50%. Both strategies were initially considered as equivalent.

In December of 2002, the Committee on Obstetrical Practice of The American College of Obstetricians and Gynecologists adopted the new CDC recommendation that obstetrical providers adopt a culture-based strategy in newborns. The risk approach is deemed by the CDC to be no longer an acceptable alternative except for circumstances where culture results are not available before delivery. Laboratories must process GBS cultures correctly using recommended selective broth media (Todd-Hewitt broth supplemented with either gentamicin and nalidixic acid or colistin and nalidixic acid). Culture specimens should be collected by swabbing the vaginal introitus, followed by the rectum, using either the same swab or two separate swabs. A speculum should not be used for culture collection. Swabs should be inserted into a non-nutritive transport medium.

Prior to 1996, it had been demonstrated that the universal administration of penicillin to all neonates would profoundly alter, but not totally eliminate, the incidence of ensuing neonatal group B streptococcal disease. The switch from a pediatric-directed approach for GBS early-onset disease to an obstetrical-directed approach was justified argumentatively by the significant maternal morbidity caused by GBS at parturition.

In terms of risk-benefit analysis, the justification has been less clear. Both penicillin and ampicillin carry with their administration the risk of anaphylaxis. The risk of fatal anaphylaxis has been estimated at 1 per 100000. The risk of non-lethal allergic reactions is a concomitant consideration. Siegel and Cushion have contended that, unlike in pregnant women, anaphylaxis has not been described in a newborn.

Wendel *et al.* have used combined intrapartum antibiotics based on both risk-factors and culture surveillance with universal neonatal penicillin administration effectively. These investigators contend that almost 1400 neonates could receive single dose prophylaxis for the cost of a single successful treatment of one GBS affected baby. If society's mandated goal on zero cases of early-onset GBS is to be met, it will require such a combined pediatric and obstetrical approach.

DIAGNOSIS

A presumptive identification of the organism can be made if a Gram smear reveals Gram-positive cocci growing in chains. Definitive diagnosis of maternal infection is contingent on laboratory procedures.

The group B organisms are characterized by their ability to:

(1) hydrolyze sodium hippurate;
(2) grow on 40% bile agar;

(3) produce a pH of 4.2–4.8 when grown in a 1% glucose broth;
(4) be partially resistant to bacitracin; and
(5) produce hemolysis on blood agar plates.

In contrast to the group A streptococci, they do not dissolve human fibrin. The organisms are distinguished from group D streptococci by their *in vitro* sensitivity to methicillin. Nevertheless, despite these diverse biologic characteristics, the ultimate identification of the organisms is contingent on the demonstration of a positive precipitant reaction by group B anticarbohydrate antiserum.

The highest incidence of GBS can be achieved when a selective medium such as Todd-Hewitt broth with sheep blood, nalidixic acid, and gentamicin are used. Commercially available options include Trans-Vag broth supplemented with 5% defibrinated sheep blood or LIM broth. When non-selective culture plates are used for bacterial isolates, colonization rates as low as 4–5% are observed. With the use of selective media which eliminate endemic overgrowth, colonization rates of 14–24% are identified.

Probability of identifying GBS is influenced by the site of bacteriological sampling. Cervical cultures are not ideal. When attempting to identify the presence or absence of GBS, samples from the vaginal introitus and the rectum should be obtained. Patients with high GBS replication ($>10^8$ cfu) will have both vaginal and rectal colonization. Positive vaginal and rectal or urine cultures for GBS potentially identify a gravida at significantly augmented risk for neonatal and/or maternal infection complications.

Several rapid diagnostic tests have been developed to make a presumptive diagnosis based on detection of group B or type-specific polysaccharide antigens in serum, urine or cerebrospinal fluid by means of monoclonal antibodies or hyperimmune antisera. These tests include countercurrent immunoelectrophoresis, latex particle agglutination, staphylococcal coagglutination, and enzyme immunoassay. The specificity and sensitivity of these tests are significantly enhanced if specimens are preincubated for 4–12 hours before utilization. Use of latex agglutination or enzyme-linked immunosorbent assay (ELISA) can significantly reduce the time required for definitive diagnosis of the GBS. Concentrated urine is a valuable specimen for the detection of the presence of specific group B antigen in neonates.

Neonatal clues to the possibility of early-onset disease include the following:

(1) identification of Gram-positive cocci in gastric aspirates;
(2) a low peak ventilatory pressure on mechanical ventilation; and
(3) repeated episodes of transient apnea or shock in the first 24 hours.

A definitive diagnosis of neonatal disease is again contingent upon bacteriologic identification.

The principal shortcoming of most rapid diagnostic tests has been their sensitivity. Skoll *et al.*, comparing the sensitivity of a latex agglutination assay (Striptex) and a solid-phase immunoassay (Equate Strept B test), found these sensitivities to be 15.1% and 21.5%, respectively. Both tests were highly specific. In general, for a rapid diagnosis test to be positive, at least 5×10^6 cfu needed to be present. These tests have their value in identifying gravidas with heavy colonization. To increase sensitivity, it is advocated that specimens be incubated in appropriate broth culture media for 4 to 6 hours and then

tested. The vaginal Gram stain lacks sensitivity, specificity, positive predictive value, and negative predictive value.

Confronted with a gravida with labor or rupture of membranes before 37 weeks of gestation at significant risk of preterm delivery, it is recommended that vaginal and rectal GBS cultures be obtained and appropriate antimicrobial prophylaxis be initiated. If at 48 hours, GBS is not identified, the antibiotic therapy can be terminated.

THERAPY

Penicillin is the drug of choice for both maternal and neonatal disease when the pathogen is the group B streptococci; however in cases in which risk factors dictate antibiotic administration, because of the bacterial pathogenic spectrum which can function under these circumstances, ampicillin or, in selected cases, a cephalosporin becomes the drug of choice under best fit for spectrum doctrine. Large initial doses of ampicillin (2 g loading dose followed by 1 g every 4–6 hours) are frequently required because of the necessity for the drug to traverse the placental or blood-brain barrier.

If the mother is penicillin-allergic, two alternate prophylactic regimens have been advocated: clindamycin, 900 mg IV every 8 hours until delivery, or erythromycin, 500 mg IV every 6 hours until delivery. Unfortunately, neither clindamycin nor erythromycin achieve category coverage for GBS.

The placenta is composed of ectodermal cells, a basement membrane, mesodermally derived tissue, another basement membrane, and fetal endothelial cells. The only other embryologic structure in the human body derived from ectoderm and mesoderm as opposed to mesoderm and endoderm is the choroid plexus. Not surprisingly, the antibiotic transports across these two membranes strongly parallel each other. The factors governing antibiotic transport across the placenta are:

(1) molecular size;
(2) degree of ionization;
(3) lipid solubility; and
(4) degree of protein binding.

Both penicillin G (pKa=2.8 for its free carboxylic-acid group) and ampicillin (pKa=2.5 for its free carboxylic-acid group and pKa=7.2 for its free amino group) are highly ionized (>99.9%) under physiologic conditions.

Both penicillin and ampicillin antibiotics exhibit only moderate lipophilicity. The oil/water partition coefficient (Ko/w) are 0.55 and 0.16 for penicillin G and ampicillin, respectively (isobutanol vs. pH 7.4 aqueous buffer).

Penicillin G is moderately bound to albumin in the sera of normal and pregnant subjects (65% bound compared with ampicillin’s 20%). To be pharmacologically active, an antibiotic must exist in its unbound state. The amount of antibiotic available for transport in a given time is a direct function of the concentration of free drug. Once the antibiotic is removed by transport, the equilibrium between bound and unbound drug is re-established. The free drug entering the fetal vascular compartment and amniotic fluid is once again subjected to similar protein binding interactions which reduce the amount of antibiotic available for biologic activity. One of the keys to effective in *utero* therapy

concerns how much pharmacologically active antibiotic appropriate to the bacteria in question can be delivered in a relatively limited time.

Penicillin G is slightly superior to ampicillin for the beta-hemolytic streptococci; however this superior minimal inhibitory concentration (MIC) for the betahemolytic streptococci does not necessarily translate into biological significance. Both drugs have been highly effective against GBS in clinical trial. The clear difference between penicillin G and ampicillin is the latter's extended spectrum for Gram-negative bacteria, specifically *Escherichia coli, Proteus mirabilis, Salmonella* species, enterococci, *Listeria monocytogenes*, and *Haemophilus influenzae*.

One of the reasons advanced for the use of penicillin over ampicillin is the statement that ampicillin selects for resistant bacteria. The concept of ampicillin's selecting for resistance emanates from a case series published by McDuffie *et al*. These authors reported 4 cases of Enterobacteriaceae chorioamnionitis in gravidas who had received ampicillin prophylaxis for premature rupture of the fetal membranes and GBS carriage. Three of the isolates were *E. coli*. The fourth case was due to *Klebsiella pneumoniae*. Two of the resultant neonates died with fulminant perinatal septicemia. The use of ampicillin identified resistant bacteria, but did not induce that resistance. Had penicillin been used, the same bacteria would have been isolated.

If an antibiotic is used against a bacterium whose spectrum of susceptibility is not encompassed by that drug, one cannot anticipate having a true biologic effect. Approximately 35–40% of all current *E. coli* isolates are resistant to ampicillin. This resistance is mediated primarily by the presence of significant quantities of betalactamases within the periplasmic space. More than 95% of all *K. pneumoniae* isolates are similarly inherently resistant to ampicillin. When isolated instances of disease due to Enterobacteriaceae occur in the face of ampicillin therapy, the probability is that the same pattern of disease would have been observed had penicillin been given.

If high risk criteria are used to determine whether or not prophylactic antibiotic is given, ampicillin owing to its partial coverage for the Enterobacteriaceae should be used. The risk factors which select for perinatal septicemia due to the Enterobacteriaceae are virtually identical to those which select for GBS septicemia (prolonged rupture of the fetal membranes, urinary tract infection, maternal fever, prematurity).

If amnionitis or chorioamnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be effective against GBS should replace GBS prophylaxis.

Recommended antimicrobial regimens

Penicillin is the preferred choice for intrapartum prophylaxis. For the reasons delineated, the alternative use of ampicillin is advocated (Table 41.3).

Therapy of gravidas with a history of penicillin-hypersensitivity is complicated by the presence of significant resistance to both clindamycin and erythromycin. Up to 155 of GBS isolates are resistant to clindamycin. Resistance to erythromycin can be as high as 25%. An isolate resistant to erythromycin, but susceptible to clindamycin, may still have inducible resistance to clindamycin. The severity of the hypersensitivity reaction to penicillin needs to be carefully evaluated penicillin-allergic gravidas who have experienced immediate hypersensitivity to penicillin, gravidas with asthma, and gravidas

with beta-adrenergic-blocking agents are candidates for vancomycin prophylaxis. For gravidas with a history of

Table 41.3 Recommended antimicrobial prophylaxis regimens for perinatal group B streptococcus (GBS) disease prevention

Recommended: Penicillin G, 5 million units IV initial dose,then 2.5 million units IV every 4 hours until delivery
Alternative: Ampicillin, 2 g IV initial dose, then 1 g IV every 8 hours until delivery
Penicillin-allergic gravidas
GBS susceptible isolate: Clindamycin, 900 mg IV every 8 hours until delivery; or Erythromycin, 500 mg IV every 6 hours until delivery
Clindamycin/erythromycin resistant GBS:
Vancomycin, 1 g IV every 12 hours until delivery; Vancomycin is reserved for women at high risk for anaphylaxis. For gravidas with other than immediate hypersensitivity reactions, cefazolin, 2 g IV Initial dose, then 1 g every 8 hours until delivery is advocated.

other than that of an immediate hypersensitivity reaction, cefazolin is preferred over vancomycin.

In the future, greater emphasis will be placed on antibiotic selection which maximizes fetal/neonatal therapy. Intravenous administration of penicillins in high doses is advocated in order to achieve higher intraamniotic drug concentrations. Erythromycin does not effectively traverse the placental barrier. Selected second- and third-generation cephalosporins penetrate into amniotic fluid in higher effective concentration than cefazolin.

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42
Group C beta-hemolytic streptococci *(Streptococcus milleri)*

Streptococci of the milleri group are part of the normal flora of human mucous membranes. These streptococci have also been reported to be significant pathogens. Like other mucosal streptococci, they may cause infective endocarditis; unlike other mucosal streptococci, however, they have also been repeatedly associated (more frequently in men than in women) with serious suppurative infections. Evidence for the pathogenicity of the *Streptococcus milleri* group is scattered and mainly circumstantial. Although the organisms are found in a high proportion of certain suppurative infections, other bacteria are often present as well. Successful treatment of these infections with surgery and broad spectrum antibiotics is not indicative of any specific etiology. '*Streptococcus milleri*' is an unofficial name that has been applied to a group of streptococci which, although basically similar, show various hemolytic, serological, and physiological characteristics. Head and neck infections and pneumonia are most often associated with beta-hemolytic strains, and bacteremia, gastrointestinal and urogenital tract infections with alpha-hemolytic strains. The species name *Streptococcus anginosus* has recently been recognized as the approved name for these organisms. Streptococci known as *S. milleri* have been implicated as etiologic agents in a variety of serious purulent infections, but because of their heterogeneous characteristics, these organisms may be unrecognized or misidentified by clinical laboratories.

Streptococcus milleri is unique among the streptococci because it produces abscesses. An infection caused by *S. milleri* often has its genesis in the gastrointestinal tract. Its isolation from pus or blood cultures is clinically relevant. The identification of *S. milleri* from blood cultures suggests the possibility of serious purulent infection, whose source may lie in the gastrointestinal tract. *S. milleri* differs from other group C beta-hemolytic streptococci and in particular *Streptococcus equisimilis* by the appearance of human Fc (gamma) receptors. The majority of hemolytic strains of *S. milleri* produce hyaluronidase. There is a strong positive correlation between hyaluronidase production and isolation of the strain from internal abscesses. Strains isolated from patients with endocarditis tend to be uniformly no hyaluronidase producers. Demonstration of hyaluronidase production in isolates from blood cultures should alert the physician to the possibility of deep seated abscess.

DIAGNOSIS

Definitive diagnosis is based upon bacteriological isolate. The presence or absence of beta-hemolysis and hyaluronidase production is important. Latex agglutination will

identify 94–96 isolates of group C beta-hemolytic streptococci. Alpha-hemolytic streptococci in this group tend to be discarded as ‘normal flora’.

Microbiologists and physicians need to become aware of the group C streptococci. The heterogeneous nature of this group of streptococci does mean that laboratories will have to use a combination of antigenic, physiologic, and hemolytic characteristics to identify these pathogenic streptococci.

CLINICAL SPECTRUM IN OBSTETRICAL AND GYNECOLOGICAL PATIENTS

Streptococcus milleri functions as both a class II and III anaerobe. In gynecological patients, *S. milleri* has produced tubo-ovarian abscess and spontaneous necrotic cutaneous infections. The bacterium is frequently isolated in patients with active perineal suppurative hidradenitis. Highet *et al.* reported that its presence is significantly associated with disease activity and its disappearance significantly correlates with clinical improvement. In this clinical setting, *S. milleri* frequently co-functions with anaerobic bacteria or *Staphylococcus aureus*. When a bacteremia is induced, metatastic hepatic abscesses may ensue. *Streptococcus milleri* can function as a significant perinatal pathogen. A number of fatal perinatal septicemias due to this bacteria have been described.

THERAPY

‘Streptococci milleri’ strains have minimal inhibitory concentration MIC for penicillin G between 0.015 and 0.12 jLLg/l. Treatment consists of drainage by laparotomy or percutaneous aspiration combined with approximately six weeks of penicillin administration. Patients with liver abscesses who receive metronidazole may not respond if *‘S. milleri’* is the infecting organism. Physicians need to recognize that these microorganisms as a group are able to cause serious infections that may require prolonged treatment and/or surgical drainage of abscesses.

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43
Enterococci and group D streptococci

Enterococci belong to the Lancefield group D streptococci. In contrast to other groups of streptococci, the wall of the group D antigen is not a carbohydrate but rather a glycerol teichoic acid containing glucose and D-alanine. The enterococci need to be distinguished from the non-enterococcal group D species and to be classified as a separate genus. They have neither the physiological characteristics nor the antibiotic sensitivities of *Streptococcus bovis* and *Streptococcus equinus*. The enterococci can be subdivided on the basis of biochemical reactions into *Streptococcus faecalis* (85% to 90%), *S. faecium* (5% to 15%), and *S. durans*. The enterococci constitute part of the normal flora to the oral cavity, colon, gallbladder, anterior portion of the urethra, endocervical, and vaginal perineal areas of women.

GENITAL TRACT INVOLVEMENT

Being indigenous to vaginal flora (particularly in multiparous women and women with cervical disorders), the enterococci not only are key players in the anaerobic progression, but are capable of functioning as significant pathogens. Bohnen *et al.* reported that the addition of the enterococci to an inoculation of *Bacteroides fragilis, Escherichia coli, Clostridium perfringens* and 10% barium sulfate led to a higher mortality and/or larger abscess formation than did inoculation without *S. faecalis*. The bacterocins elaborated by the enterococci have little effect on the Bacteroidaceae. The growing emergence of their role as monoetiological pathogens is tied to current antibiotic usage. Serious enterococcal super-infections occur in patients receiving broad-spectrum antibiotics, particularly cephalosporins. Yu reported nine cases of enterococcal superinfection or colonization following moxalactam usage.

URINARY TRACT INFECTION

The enterococci are encountered with appreciable frequency in infections of the urogenital tract in women with gynecologic disease. In a CDC survey of nosocomial infections, enterococci accounted for 13.9% of urinary tract infections (UTIs). Most frequently, these patients have a history of prior instrumentation or the presence of drains in the urogenital tract. Antibiotic prophylaxis in women with recurrent UTIs tends to increase *S. faecalis* infection owing to prior antibiotic selection. Women who have recurrent UTIs have been found to have a higher rate of introital colonization with *S. faecalis* than non-infection-prone controls.

PERINATAL SEPTICEMIA

Both enterococci and nonenterococci group D streptococci can produce a perinatal septicemia which is clinically significant. Bavikatte *et al.* have reported nine cases of neonatal sepsis caused by the enterococci. The group D streptococci account for about 4% of all septicemic bacterial isolates in most large series. When disease occurs shortly after birth, the principal manifestation is that of respiratory distress. Without aggressive antibiotic therapy, disease may progress to apnea and the induction of shock in the first 24–48 hours of life.

DIAGNOSIS

Enterococci are oval Gram-positive cocci in pairs or short chains. On agar media, the colonies are larger than most of the other streptococci (1 to 2 mm in diameter) and of 'buttery' consistency. On blood agar, *S. faecalis* may be beta-hemolytic, but is usually non-hemolytic (gamma) or rarely alpha-hemolytic, *E. faecium* is usually

Table 43.1 Advocated antibiotic regimens in the treatment of infections with the group D streptococci

Drug of choice Ampicillin and an aminoglycoside
Other antibiotics effective against 'community acquired' enterococci (listed in order of decreasing efficacy): Penicillin and an aminoglycoside (alternate drugs of choice) Trimethoprim-sulfamethoxazole Vancomycin and an aminoglycoside (reserved for serious community acquired infection)

alpha-hemolytic, and the remainder of the enterococcal species are generally beta-hemolytic.

Enterococci are able to grow in media that contains 6.5% NaCl, 40% bile, or 0.1% methylene blue. They can survive in media at 60ºC. These conditions are referred to as Sherman's criteria. A presumptive recognition of enterococci is made on the basis of their ability to grow in a bile-esculin medium. Definitive identification is then made by the growth of bile-esculin positive streptococci in 6.5% NaCl solution. Neomycin blood agar in medicine allows for identifications of vancomycin-resistant enterococci.

THERAPY

Current antimicrobial regimens for serious enterococal infections consist of a combination of ampicillin or penicillin G, or vancomycin plus streptomycin or gentamicin.

The non-community-acquired enterococci are relatively resistant to penicillin G and ampicillin. The mechanism for the enterococcal resistance may be the group-specific lipoteichoic acid antigen and its effect on the autolytic enzyme system.

Carbenicillin and ticarcillin are about four-fold less active against enterococci than penicillin G, piperacillin, or ampicillin. The minimal inhibitory concentrations (MIC) of the vast majority of cephalosporins are too high to make these agents clinically useful. Tetracycline, erythromycin, and clindamycin do poorly against the *Enterococcus* genus and select group D streptococci.

Though both the enterococci and select group D streptococci are relatively resistant to the aminoglycosides, their addition to ampicillin, penicillin or piperacillin or vancomycin results in a synergistic enhancement resulting in more rapid and complete bactericidal activity. The synergism between cell wall active antibiotics and aminoglycosides has been explained by the increased uptake of aminoglycosides in the presence of cell wall bactericidal agents.

Ampicillin, mezlocillin, and piperacillin are the most active antibiotics against community-acquired species of enterococci (Table 43.1). Vancomycin/gentamicin is the drug of choice for the nosocomial isolates of the enterococci.

VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE)

The incidence of vancomycin resistance among enterococci, and *E. faecium* in particular, has increased sharply in the last few years. This shift toward infection with resistant Gram-positive organisms is thought to be the consequence of certain features specific to the intensive care setting: a high concentration of severely compromised patients; continued use of indwelling devices and invasive procedures; and wide-spread, empiric use of antimicrobial agents directed against Gram-negative bacilli (particularly the cephalosporins).

Risk factors associated with VRE infection and colonization are vancomycin and cephalosporin use, but numerous patient-related factors also contribute. Multivariate analyzes found that the duration of hospitalization (≥7 days), intrahospital transfer between floors, use of antimicrobials (i.e. vancomycin and third-generation cephalosporins), and duration of vancomycin use (≥7 days) were independently associated with VRE infection or colonization.

Most VRE are resistant to all available antimicrobial agents. The resistance genes are transmitted on transposons, so the potential for dissemination to other species is significant. The risk of transfer of vancomycin resistance to staphylococci is a real possibility and has been achieved in the laboratory. Prolonged colonization occurs with VRE.

Although no antimicrobial agents are currently available for VRE infections, VRE line-related bacteremiae could be treated by line removal alone, surgical site infections and abscesses could be managed by surgical debridement and drainage without specific antimicrobial agents against VRE, and UTIs could be resolved with nitrofurantoin or removal of Foley catheters. The ideal drug regimen for the treatment of VRE is unknown. Removal of foreign devices, debridement, and surgical drainage seem to be important in the resolution of VRE infections. Although resistant strains appear to arise from the

patient's endogenous flora, VRE may be spread through direct contact with contaminated environmental surfaces and hands of caregivers. Published guidelines for preventing such spread suggest implementing infection-control practices and vancomycin restrictions.

The prevention and control of resistant enterococci is a major challenge that is best met by a combination of active infection control measures and restriction of broad-spectrum antibiotic use. The failure to identify, isolate, and adhere to infection control measures when caring for VRE-colonized patients dooms to failure any means to control its spread. Control of vancomycin use alone is unlikely to greatly affect the number of patients at risk for VRE colonization. Measures that can be taken to prevent the development of bacterial resistance in ICUs include strict adherence to infection control policies and asepsis, and rational use of antibiotics.

Hospital-wide outbreak of VRE

Limiting the use of vancomycin and effective use of barrier methods to limit nosocomial spread are the cornerstones of prevention and control; however in most instances, once VRE colonization of a unit occurs, these measures have limited success in preventing additional patient recruitment and clinical outbreak. Despite infection control practices for vancomycin resistance, gastrointestinal colonization of new patients occurs. In an attempt to control an outbreak, investigators altered the antibiotic formulary by restricting the use of cefotaxime and vancomycin and adding beta-lactamase inhibitors to replace third-generation cephalosporins. After 6 months, the average monthly use of cefotaxime, ceftazidime, vancomycin, and clindamycin had decreased by 84%, 55%, 34% and 80%, respectively ($P<0.02$). The point prevalence of fecal colonization with VRE decreased from 47% to 15% ($p<0.001$), and the number of patients whose clinical specimens were culture positive also gradually decreased. A change in antibiotic use may significantly affect VRE outbreaks when previous measures have failed.

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44
Group F streptococci

The group F streptococci belong to the *Streptococcus milleri* group which includes *S. anginosus, S. consellatus*, and *S. intermedius*. The *S. milleri* have a property which differs from classical streptococcal infections. They pro-duce suppurating lesions. They have been isolated from Bartholin's gland abscesses, wound infections as well as brain and hepatic abscesses. Inflammatory disease such as arthritis and meningitis have been described as a consequence of hematogenous metastatic spread.

The group F streptococci tend to be primarily constituents of bowel and oropharyngeal bacterial flora. Of 279 bactrin-resistant streptococci obtained from children and adolescents with pharyngitis, 35 were group F. The group F beta-hemolytic streptococci are not a common cause of disease, but when it does occur, its consequences are often significant. Bacteremia due to the group F streptococci may produce disease in distal organ systems. DeAngelo *et al.* reported a case of bacteremia in a patient following manipulation of a three-day-old vulvar abscess.

During the decade 1970–1980, group F streptococcal bacteremia accounted for 2% of the beta-hemolytic streptococci isolated from all patients hospitalized with bacteremia at Mayo Clinic affiliated hospitals.

Almost all isolates of group F streptococci are extremely sensitive to the penicillin antimicrobials (<0.1 μg of penicillin/ml). This sensitivity to penicillin coupled with its rarity as a constituent of the genital flora may have masked perception of the group F streptococci as a potential perinatal pathogen. Wells and Kenney in 1980 reported a case of prolonged rupture of membranes which occurred at 37 weeks gestational age in which the ensuing progeny developed subsequent perinatal pneumonia. Group F streptococci were isolated from skin, cord, blood cultures, nasopharynx, throat, stomach, tracheal aspirates and fetal surface of the placenta. Hill *et al.* reported a case of perinatal bacteremia/septicemia in a premature infant with prolonged rupture of the fetal membranes and anaerobic amnionitis.

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45
Group G beta-hemolytic streptococci

In 1933 Rebecca Lancefield, by means of a precipitin reaction, serologically identified and grouped the streptococci according to their cellular carbohydrates. Initially, she identified five antigenically distinct streptococcal groups and designated them A, B, C, D, and E. Since these earlier observations, eighteen groups, A through H and K through T, have been identified. The groups A, B, C, D, and G are the principal groups associated with human disease.

Like the group A beta-hemolytic streptococci, the group G streptococci appear to function as exogenous pathogens for the female genital tract. Structurally and pathophysiologically, both groups are similar to the group A streptococci. Immunofluorescent techniques have demonstrated cross-reactivity between the cell membranes of groups A, C, and G, implying antigenic similarities. All three groups share the propensity for involving the skin, the respiratory tract, and the female genital tract. Despite these similarities, infection with group G streptococci is not followed by nonsuppurative complications (acute rheumatic fever and acute glomerulonephritis). The group G streptococcus is considered a normal constituent of the female genital tract bacterial flora.

With the exception of cutaneous disease superimposed upon pregnancy or occurring in a gynecologic oncologic patient, the principal clinical manifestation is postpartum endometritis. Although most cases of puerperal sepsis with group G streptococci are described as mild, several deaths have been reported. The typical pattern of onset is that of a spiking temperature rising to 39.5–41ºC. Like the group A streptococcus, the group C and G streptococci are extremely sensitive to penicillin G. The anticipated response to effective therapy is a rapid defervescence over a 24- to 48-hour period.

The group G streptococci are recognized as a cause of perinatal septicemia. Infection occurs primarily in premature or low birthweight infants and in the setting of prolonged rupture of the fetal membranes. Early aggressive therapy is the principal factor selecting for outcome. Once complications such as progressive respiratory distress, shock, and/or disseminated intravascular coagulation occur, the prognosis is almost invariably poor.

Disease due to the group G streptococcus can occur as a complication of gynecologic surgery. Recurrent cellulitis has been reported as a rare complication of radical hysterectomy and radiation therapy. Auckenthaler, in 1983, described five patients with gynecologic malignancies treated with radiation therapy who developed cellulitis and bacteremia due to group G streptococci. The initial surgical wound and impaired lymphatic drainage were thought to be predisposing factors.

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46
Chlamydia trachomatis

Members of the genus *Chlamydia* are obligatory intracellular Gram-negative parasites. The infectious particles form elementary bodies and have an overall diameter of 325 μm. Pinocytosis of the infectious elementary bodies by a cell results in their transformation into initial bodies which in turn congregate to form actively dividing inclusions (reticular bodies). These reticular bodies, visible under light microscopy, appear to divide by a simple pinching-off process similar to that observed with other Gram-negative organisms. Both RNA and DNA have been identified in them. Biochemical analysis reveals the presence of muramic acid, which is an important mucoprotein of bacterial cell walls. Chlamydial particles parasitize their host cells for the ATP required for metabolic activity and transformation of the initial/reticular bodies into infectious elementary bodies. Chlamydial infection of the host cell finally leads to cell death and release of the newly synthesized elementary bodies.

Chlamydia organisms can be segregated into subgroups (A and B) on the basis of whether or not the intranuclear inclusion bodies produced in tissue culture cells will stain with iodine. *Chlamydia psittaci* (subgroup B) organisms, which are responsible for ornithosis, do not stain with iodine, in contrast to those of the A subgroup (Figure 46.1). The *Chlamydia trachomatis* (subgroup A) strains that infect humans can be differentiated into lymphogranuloma venereum strains (LGV or L strains) and the trachoma-inclusion conjunctivitis (TRIC) agents. Most of the ocular infections due to the TRIC agents, in regions where trachoma is epidemic, belong to the serologic types A, B, BA, and C. In those areas where trachoma is endemic, trachoma infections are due to serotypes D through K. These latter serotypes primarily infect the female genital tract and appear to be sexually transmitted. However, the eye occasionally is infected from the female genital tract. A great deal of confusion exists concerning nomenclature. The TRIC

Table 46.1 The spectrum of clinical disease attributable to D, E, F, G, H, I and K strains of *Chlamydia trachomatis*

Females	***Neonates***
I. Mucopurulent cervicitis	I. Inclusion conjunctivitis
II. Abacterial urethritis	II. Pneumonia
III. Acute salpingitis (stages I and II)	
IV. Curtis-Fitz Hugh syndrome	
V. Ectopic pregnancy	
VI. Endometritis	

VII. Preterm deliveries??

VIII. Adult inclusion conjunctivitis

delineates primarily ocular strains. The genital strains of chlamydia tend to be referred to by the genus name, *Chlamydia*.

FEMALE GENITAL TRACT INVOLVEMENT

The name chlamydia is derived from the Greek work ‘chlamys’ which means ‘to cloak’. The major focus has been on the strains of *C. trachomatis* which cause genital tract infection. In contrast to men with non-gonococcal urethritis or postgonococcal urethritis, women with cervicovaginal infection rarely present with specific symptoms or signs. The spectrum of clinical disease attributed to the genital strains of *C. trachomatis* which impact on women and their progeny is listed in Table 46.1.

Asymptomatic carriage

Chlamydia trachomatis can be isolated from 12–28% of women attending clinics for sexually transmitted disease (STD), exclusive of those women who have either gonorrhea or are the female sexual contacts of men with non-gonococcal urethritis. These figures are in contradistinction to the 1–4% isolate rate achieved in control populations. The genital strains of chlamydia can be

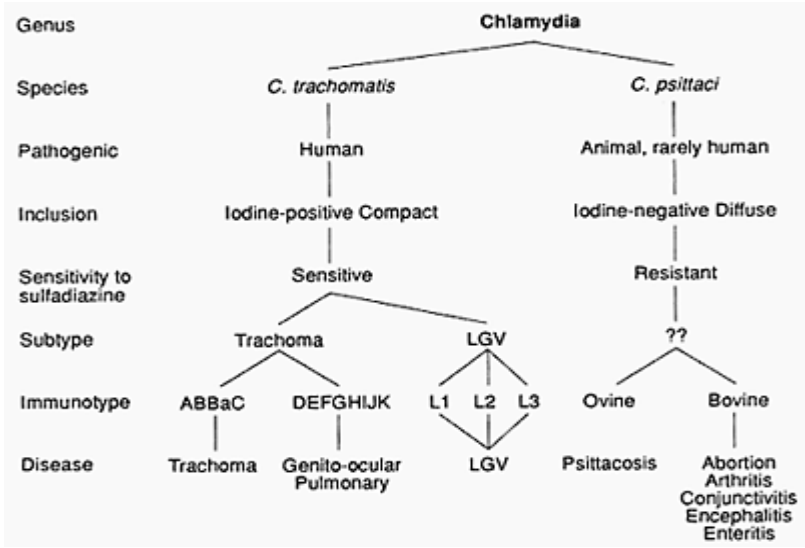

Figure 46.1 Summary of the chlamydiae characteristics

isolated from 4–7% of women who have cervical dysplasia or are attending a women's health clinic Fewer than 1% of women of advanced age undergoing selective cancer screening appear to harbor the organism.

Among chlamydia-positive women identified from women attending gynecological clinics, 55–75% will be subjectively asymptomatic. In the absence of appropriate antimicrobial therapy, the organism may persist for months and provide a continuing reservoir for chlamydial infection. Latency has long been recognized as a common state in chlamydial infection. *Chlamydia* utilizes cellular metabolites, amino acids, and nucleotides. The failure to supply the agent with essential growth factors may lead to a state of latency.

The prevalence of infection caused by *C. trachomatis* now exceeds that caused by *Neisseria gonorrhoeae*. In the United States, about three million individuals are infected annually. The changes with the sexual revolution and the availability of alternate forms of contraceptives other than the condom have resulted in chlamydia becoming the most important STD for women. Its importance is in part due to the fact that occult or subacute forms of infection are fully capable of destructive sequelae.

Wide disparity in the rate of chlamydial infection have been observed in different populations. Certain groups of women are at apparent higher risk. Women who come from a disadvantaged socioeconomic background and have multiple sexual partners are at highest risk. Age is also a risk indicator but only insofar as it connotes the high risk factors involving augmented sexual activity. In women of child-bearing age, the anticipated incidence of positive cultures of single, unmarried, teenage gravidas may approach 14%. The incidence of gravidas over the age of 35 coming to chorionic villus sampling because of age is less than one-half of one percent. A 4–9% incidence is about average in most balanced obstetrical populations.

Mucopurulent cervicitis

When clinically overt, the most common presentation of chlamydial infection is mucopurulent cervicitis. Mucopurulent cervicitis is defined as the presence of mucopus at the endocervix in a female with a vaginal discharge and/or the demonstration of 10 or more polymorphic neutrophils per field at a magnification of ×100 per cervical mucus. Approximately 20% of the women with mucopurulent cervicitis will be demonstrated to have infection with *C. trachomatis*. Speculum examination of the cervix reveals inflamed ectopions present which readily bleed to touch. Particularly in patients who had previously been on low-dose progestational oral contraceptives, patients with a history of chlamydial endometritis will persist with a history of intramenstrual bleeding with or without pelvic pain suggestive of Krettek's Syndrome. (Figure 46.2) In retrospect, it is probable that some of the intramenstrual symptomatology associated with the intrauterine contraceptive device (IUD) was probably also due to *C. trachomatis* endometritis and not necessarily to IUD-related chronic anaerobic endometritis. One-third of women with mucopurulent cervicitis will have a second STD pathogen identified.

The cervicitis may be sufficiently extensive so as to mimic vulvovaginitis. Among couples seen in STD clinics, it is not uncommon to have the male in one room with non-gonococcal urethritis while, in another room, the woman presents with a clinically

significant vaginal discharge for which none of the traditional vulvovaginal pathogens can be discerned or isolated.

While both *C. trachomatis* and *Neisseria gonorrhoeae* can cause mucopurulent cervicitis, in most cases neither organism can be isolated. The sexual consorts of women with mucopurulent cervicitis should be evaluated for STDs and managed appropriately.

Abacterial urethritis

Chlamydia trachomatis has been proposed as one of the etiologic agents for a bacterial urethritis or the so-called 'urethral syndrome'. Women with positive cervical cultures for *C. trachomatis* frequently have concomitant urethral colonization. These women with positive isolations of *C. trachomatis* from the urethra more often have urethral symptoms of dysuria and frequency compared with those women with positive isolations from cervix alone. Urethral involvement seldom occurs in the absence of cervical infection. It is frequently silent, producing no signs or symptoms of urethritis.

Chlamydial salpingitis

Chlamydial salpingitis has always been part of the venereal disease spectrum. In 1732, John Astruc wrote in his book based upon observations of Parisian prostitutes of a chronic form of salpingitis which:

> *"occurs in women whose uterus is thrown into contractions by lascivious ticklings and by excess of prostitution. Many have no pain but their infection in time injures the internal surface of the uterus and its tube."*

In contrast to gonococcal salpingitis, chlamydial tubal infection appears to be a true chronic infection. Intracellular chlamydial organisms may persist in the genital tissues for extremely long periods of time and continue to produce silent progressive tubal damage unless treatment with appropriate antibiotics is instituted. When infertile patients with chlamydial antibodies are evaluated with laparoscopy, frequently no history of an illness or procedure can be elicited which could explain the presence of post-inflammatory tubal damage.

Cultural and serologic data have built an extensive case for *C. trachomatis* as both an etiologic agent and a potential co-pathogen in acute salpingitis. As in the male with gonococcal urethritis, chlamydial cervicitis is not infrequently concomitantly present in patients with gonococcal endometritis-salpingitis. Mardh *et al.* have recovered *C. trachomatis* from six out of 20 specimens

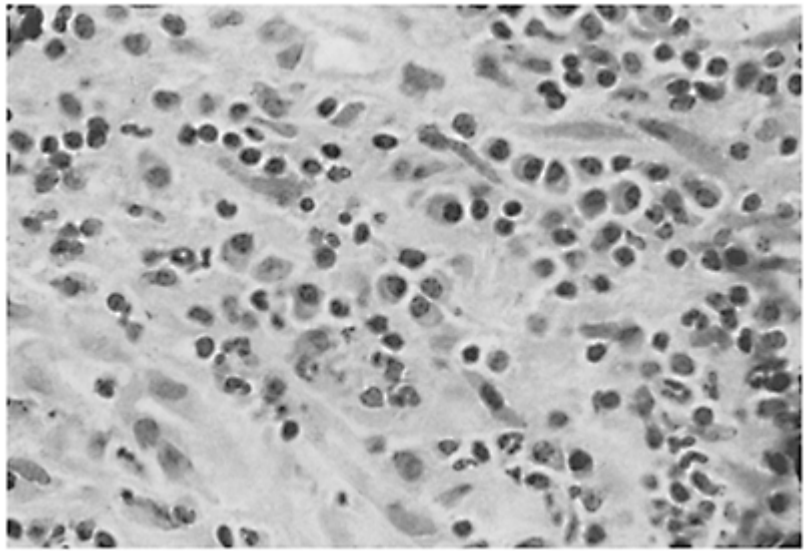

Figure 46.2 Endometrial biopsy from a patient with breakthrough bleeding demonstrating a mononuclear cell stromal infiltrate composed of both lymphocytes and plasma cells within the inflammatory infiltrate (hematoxylin and eosin, ×400)

from fallopian tube aspirations from women with acute endometritis-salpingitis compared with none from the 12 controls.

Thirty percent of women with acute salpingitis from whom *C. trachomatis* is recovered have concomitant gonococcal endocervicitis. Ripa *et al.* demonstrated that 86 of 143 patients (62%) with acute salpingitis had significant chlamydial IgG antibodies in their serum. The magnitude of antibody correlated with the staging of disease, the highest geometric mean titers being found in women with the most severe grade of salpingitis.

In contrast to ‘classical pelvic inflammatory disease’, chlamydia disease tends to be more occult. Often only vague peritoneal pain precipitated by jarring movements is the prime motivating factor for the patient to seek medical attention. Characteristically, the temperature is less than 38 degrees Celsius, and the only significant finding on pelvic examination is cervical motion tenderness and varying degrees of cervicitis.

The role of *Chlamydia* in acute salpingitis is poorly understood. Can *C. trachomatis* initiate infection and pave the way for bacterial superinfection or does it work synergistically with other bacteria?

IUD-associated chlamydial salpingitis

In retrospect, some of the structural morbidity attributed to IUD-associated chronic anaerobic endometritis is probably due to concurrent chlamydial infection. Guderian and Trobough evaluated by laparoscopy or laparotomy 245 infertile patients for inflammatory residues; 176 patients had not used an IUD and 69 had used this form of contraception. Chlamydial antibody titers were performed on all patients. Although users had a higher overall prevalence of inflammatory residues than non-users, there was no difference in residue prevalence for either group at the same titer level. 'Residues of pelvic inflammatory disease' included a spectrum of postinfectious pelvic abnormalities ranging from severe periadnexal adhesions and tubal occlusion to mild adhesions and minimal tubal epithelial damage. No specific type of device appeared to be associated with either an increased or decreased residue frequency. 'Silent' chlamydial infections occurred with equal frequency in both users and non-users. They conclude that inflammatory residues and tubal infertility in IUD users is more probably due to either overt or silent chlamydial infections.

Similarly, Chow *et al.* have demonstrated that, while patients using IUDs have a higher prevalence of inflammatory residues than non-users, they also have a higher prevalence of chlamydial antibodies.

The increased frequency of chlamydial salpingitis in users may be a function of either increased exposure rate or increased attack rate. The IUD may increase the prevalence of upper tract disease after chlamydial exposure (increased attack rate) by modification of host defenses. On the other hand, IUD users may be exposed to *C. trachomatis* and other STDs with greater frequency than non-users (increased exposure rate).

Endometritis

The increased prevalence of a late-onset postpartum endometritis in chlamydia-positive gravidas who undergo cesarean section or voluntary termination of pregnancy has been focused upon the ability of chlamydia to produce disease in this clinical setting. While endocervical carriage of *C. trachomatis* appears to select for increased risk, most women do not develop endometritis postpartum.

The possibility that chlamydial endometritis is a distinct entity has been suggested from the studies of pelvic inflammatory disease, which have included histopathological analysis of endometrial biopsies. In one study, severe plasma cell endometritis and lymphoid follicles with transformed lymphocytes were significantly more common in those patients with recovery of *C. trachomatis* from their endometrial biopsies than in the non-chlamydial group.

A poorly recognized variant of chlamydia endometritis is Krettek's Syndrome. Krettek *et al.* described breakthrough mid-cycle bleeding in women on oral contraceptives. Classically, these patients responded to a seven- to ten-day course of tetracycline or doxycycline much in the same way as did women with menstrual irregularities secondary to IUD-associated chronic anaerobic endometritis. When done, biopsies of the endometrium have revealed the presence of a mononuclear cell infiltrate in 30–40% of patients with endocervical chlamydial infection.

Osser and Persson note a 23.2% and 14.5% incidence of endometritis and salpingitis among chlamydia-positive women in contrast to 5.7% and 0.6% in chlamydia-negative women during the first postoperative month following legal abortion by vacuum aspiration. These differences were highly significant and suggested that *C. trachomatis* may be an etiologic agent in post-abortion endometritis.

Curtis-Fitz Hugh syndrome

The 'Curtis-Fitz Hugh syndrome' is an inflammation process due to a STD pathogen which involves the supra- or intrahepatic portion of the capsule of the liver. Both Fitz Hugh and Curtis were of the opinion that the condition occurred only in women. Disease has been postulated to result from either direct extension, passage of infecting organisms up the paracolic gutters or lymphatic drainage to the liver surface. The rare occurrence of this syndrome in males has focused on the probable existence of an additional mechanism for hepatic involvement. More than half of the reported cases of Curtis-Fitz Hugh syndrome in males occurred in individuals who had experienced hematogenous dissemination. In these cases, rather than being a perihepatitis, true parenchymal involvement probably occurs.

The initial symptom is that of a dramatic, excruciating, sharp pain most intense at the level of the right lower rib margin and over the area of the gallbladder. With the suprahepatic variant, the pain may be referred to the right shoulder or the inside of the right arm. The pain is pleuritic in character being exaggerated by coughing, deep inspiration, laughing and rotational movements of the torso. Hiccups and nausea frequently accompany the pain. Vomiting may be present. The clinical presentation may also involve chills, fever, night sweats, headache and general malaise.

Initially *Neisseria gonorrhoeae* had been etiologically deemed the sole cause of Curtis-Fitz Hugh syndrome. Subsequently, through serological and culture studies, *C. trachomatis* has been documented to be an etiological agent for this entity. Wolner-Hanssen *et al.* have isolated the organism from the liver capsule. The Curtis-Fitz Hugh syndrome associated with *C. trachomatis* tends to occur most frequently in women who have had relatively recent insertion of the IUD.

OBSTETRICAL SPECTRUM OF DISEASE

The role of *C. trachomatis* as a STD and a relatively incomplete knowledge base concerning the natural history of female genital tract involvement have largely obscured the perinatal, as opposed to neonatal, impact of this organism.

Ectopic pregnancy

Fragmentary data purport that endocervical chlamydial infection is associated with a 30–40% probability of concomitant endometrial infection. Should conception occur, chlamydial fallopian tube and/or endometrial infection appears to have the potential to adversely impact on blastocyst implantation. Brunham *et al.* studied 50 women with ectopic pregnancies for serological evidence of chlamydial infection. Histological

analysis of fallopian tube tissue distant from the site of ectopic implantation was available in 41 cases. The histopathologic finding of plasma cell salpingitis in approximately one-third of women without an identified cause of ectopic pregnancy was interpreted as being consistent with the hypothesis that tubal infection was an underlying cause in this group of women.

Preterm labor

Postconceptional acquisition has been associated in some, but not all, studies with a statistically significant increase in premature rupture of the fetal membranes (PROM) and/or preterm labor. The exact mechanism by which these consequences are induced remains speculative.

Berman *et al.* studied 1204 Navajo women enrolling for prenatal care for the endocervical presence of *C. trachomatis*, *Mycoplasma hominis*, and *Ureaplasma urealyticum* cultures. Serum samples were taken at enrollment and, when possible, after 30 weeks. Although women with recent *C. trachomatis* infection (IgM titer>1:32 on either sample or IgG seroconversion) were at greater risk of low birthweight (19% [3/16]) than women with chronic infection (4.5% [6/133]; relative risk, 4.2%), this subgroup at risk was too small for valid statistical analysis.

Gravett *et al.* studied 534 gravid women for the presence of endocervical chlamydial infection. In this study, *C. trachomatis* infection was documented in 47 (9%) of the women. Cervical infection with *C. trachomatis* was independently associated with preterm PROM, preterm labor, and low birthweight. Unfortunately, the other microbiological variables and co-factors which might have contributed to adverse pregnancy outcome were poorly controlled.

In their study of pregnant women, Harrison *et al.* suggested that only the subset of women with recently acquired *C. trachomatis* infection are at risk for premature events. Only IgM-seropositive patients with *C. trachomatis* were at increased risk of preterm PROM and low neonatal birthweight.

When Sweet *et al.* re-examined the patient population reported by Schachter *et al.* and compared it with a matched controlled subject group, subjects being matched for age, race, and socioeconomic status, there was no statistical difference noted in terms of PROM, preterm delivery, amnionitis, intrapartum fever, small-for-gestational-age babies, postpartum endometritis, and neonatal septicemia. In the subset of women with recent or invasive chlamydial infection indicated by the presence of IgM antibodies against *C. trachomatis*, preterm delivery occurred in 13 of 64 IgM-positive individuals versus 8 of 99 IgM-negative individuals. The same statistics applied to PROM.

The studies published to date are less than perfect in terms of the experimental design. Too many uncontrolled variables which potentially impact on outcome exist in all studies which have purported a positive relationship between endocervical infection with *C. trachomatis*, adverse pregnancy outcomes, and those which demonstrate no difference. Incomplete demographic and microbiological profiling and flawed experimental designs allow for one to choose those studies which appeal to *a priori* biases.

NEONATAL CHLAMYDIA INFECTION

Heggie *et al.* demonstrated that, despite failure to detect chlamydial infection in exposed infants, lymphocyte-proliferative responses are greater in neonates born to infected mothers than in infants born to uninfected mothers. Such data suggest that neonatal cellular immune responses to chlamydia antigens are increased in infected mothers and that infants may acquire chlamydial cell-mediated immunity transplacentally.

The predominant focus of analysis to date has been on the periparturitional neonatal acquisition of infection. Chlamydial infections in the neonate are almost invariably the consequence of delivery through an infected birth canal.

Conjunctivitis and pneumonia are the principal two manifestations of neonatal chlamydial infection. Up to two-thirds of infants born to mothers with chlamydial genital infection will become infected and develop one or both of these sequelae.

Schachter *et al.* prospectively followed 5531 pregnant women. In this study population they identified 262 (4.7%) of women who had positive cervical cultures for *C. trachomatis*. One hundred thirty-one of the ensuing progeny were prospectively followed to ascertain the outcome of chlamydial exposure during the birth process. Culture-confirmed inclusion conjunctivitis of the newborn was seen in 23 (18%) of the infants. Chlamydial pneumonia was diagnosed in 21 (16%) at risk. *C. trachomatis* was recovered from 47 (36%) of the infants; however, 79 (60%) had serological evidence of infection. Subclinical rectal and vaginal infections were detected in 14% of the infants. Of the infants with serological evidence of perinatal chlamydial infection, half of these developed either chlamydial pneumonia or conjunctivitis.

Neonatal conjunctivitis

In contradistinction to gonococcal ophthalmia neonatorum, which usually appears within five days, chlamydial conjunctivitis usually has its onset between the fifth and fourteenth day postpartum. Premature rupture of the fetal membranes or heavy vaginal colonization appears to select for an earlier onset of disease. Unlike the gonococcus, *C. trachomatis* is not affected by silver nitrate ophthalmic drops. The effective utilization of Crede´ prophylaxis has rendered inclusion of conjunctivitis due to *C. trachomatis* the most common cause of infectious neonatal conjunctivitis. It is currently estimated that 1.1–4.4 cases occur per 1000 live births.

Approximately 44% of the progeny born to gravidas who, at the time of parturition, harbor *C. trachomatis* as a constituent of their vaginal flora will develop laboratory-proven inclusion conjunctivitis, characterized by a mucopurulent exudate. Without therapy, the disease tends to resolve spontaneously several weeks to a month after onset. In isolated instances, pseudopannus may form in the conjunctiva resulting in permanent scarring. Early therapy appears to abort any late sequelae such as scar formation or corneal vascularization. The majority of neonates with inclusion conjunctivitis will have the organism present in the trachobronchial tract and nasopharynx. While the tetracyclines are the drugs of choice for chlamydial infections, this class of antibiotics is not to be used in a pediatric population when alternative effective therapy such as

erythromycin is available. Since treatment failures will occur with topical therapy, systemic administration of antibiotics is advocated.

Topical therapy for neonatal ocular infection is not recommended. While it may eradicate ocular chlamydial infection, nasopharyngeal carriage persists which can act a source for pulmonary disease or ocular reinfection.

Occasionally, rhinitis, nasopharyngitis, tracheitis, and otitis media may be associated with chlamydial infections of the eye.

Postnatal pneumonia

Chlamydia trachomatis is responsible for 20–60% of all pneumonias during the first six months of life. Typically, the symptoms begin in the second or third week of life and gradually worsen. Characteristic presentation of chlamydial pneumonia among infants is that of a repetitive staccato cough with tachypnea. Age at diagnosis of pneumonia is typically six weeks. The infants are afebrile and without malaise. Partial nasal obstruction and mucoid discharge are often noted. Respiratory signs are usually those of tachypnea and pertussis-like cough. The chest X-ray tends to demonstrate a combination of hyperexpansion with diffuse interstitial and focal alveolar infiltrates. Auscultation reveals fine inspiratory crepitant rales. Fifty percent of infants with chlamydial pneumonia have a prior history of concomitant chlamydial conjunctivitis.

The cough and tachypnea may require weeks to clear. The rales and X-ray findings may persist for more than a month. Approximately one-half of the affected children will have a prior history or concomitant demonstration of conjunctivitis.

Specimens should be collected from the nasopharynx for chlamydial testing. Tissue culture remains the definitive standard for chlamydial pneumonia; non-culture tests can be used with the knowledge that non-culture tests of nasopharyngeal specimens produce lower sensitivity and specificity than non-culture tests of ocular specimens. Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*. An acute IgM antibody titer≥1:32 is strongly suggestive of *C. trachomatis*.

The therapy of choice is erythromycin 50 mg/kg/day orally divided into 4 doses. The effectiveness of erythromycin treatment is approximately 80%; a second course of therapy may be required.

Chlamydia trachomatis is capable of replicating on any mucosal surface, including that of the gastrointestinal tract. Schachter *et al.* have demonstrated *Chlamydia* in the vagina of female neonates.

DIAGNOSIS OF CHLAMYDIAL INFECTION

Culture and three different antigen detection tests are currently the principal diagnostic methods acceptable for screening for chlamydial infection.

The use of cell culture systems for the detection of *C. trachomatis* is the gold standard. However, the sensitivity of a single endocervical specimen may be only 70–90%. Unfortunately, cell culture is labor intensive and requires 48 hours for completion. These problems fostered the development of simplified rapid diagnostic tests which bypassed the issue of organismal viability. The first detection systems were based on either

immunodetection of solubilized chlamydia antigens (enzyme immunoassay) or direct visualization using chlamydia-specific fluorescence-conjugated monoclonal antibodies (direct fluorescent antibodies). Their sensitivity and relatively poor positive predictive values lead ultimately to their relative abandonment in favor of tests based on DNA/RNA hybridization.

Culture

While culture is the most definitive means of making the diagnosis of chlamydia, it is costly and takes at least two to three days before results are available. Although published methods are fairly standard, in practice many laboratories introduce variations that alter the sensitivity and specificity of the test.

Two major components are needed to culture for *C. trachomatis:* (1) a cell-culture system, and (2) a method to identify inclusions growing in cell culture. The cell line of choice is McCoy. Alternatively, a particular strain of HeLa cells (HeLa 229) can be used. Specimen material is centrifuged onto the cells for one hour and then incubated for two to three days in medium containing cycloheximide. Incubation can take place in individual vials with cover slips at their base or on flat-bottomed wells in plastic microtiter plates. The choice between these methods is generally dictated by the number of specimens a laboratory has to process; the vial method is slightly more sensitive and less susceptible to cross-contamination, but is more time-consuming and expensive.

For identification, either iodine stain or fluorescent antibody (FA) stain is usually used. FA stain offers the advantages of higher sensitivity and shorter processing time (two to three days) but requires a fluorescence microscope. The standard method for iodine staining requires one blind passage, which increases the processing time to four to six days. In microtiter plates, FA staining without passage appears equivalent to iodine staining with one blind passage. The most sensitive culture method currently available involves using cycloheximide-treated McCoy cells in vials in the presence of fluorescent monoclonal antibodies.

In collecting any specimen for chlamydial culture, it is imperative to avoid sampling mucopurulent exudate. *C. trachomatis* is an obligatory intracellular organism. The specimen must contain endocervical cells. Cotton swabs are not to be used because of the possible presence of cytotoxic material. Use of a dacron or nylon swab with plastic or wire shaft is advocated.

Compared with other diagnostic tests for *C. trachomatis*, the major advantage of tissue culture is its specificity. With this method, the organism can also be positively identified or saved for other marker studies such as immunotyping. Thus, culture is clearly the method of choice for research studies. It is estimated that culture has a sensitivity of 80–90%, and a specificity of 100%.

There is limited value in obtaining routine urethral cultures to aid in the diagnosis of chlamydial infections. Dunlap *et al.* used triple culture tests at each site in the evaluation of 112 women with *C. trachomatis* infection. Organisms were recovered from the cervical material from 110, urethral material from 32, and rectal material from 19. Triple swabs provided 89 (81%) of the 110 diagnoses of cervical infection; the first swab yielded 65 (59%); the second swab an additional 15 (14%); and the third an additional 9 (8%). Three sets of cervical scrapings provided 102 (93%) of 110 diagnoses of cervical

infection; the first scraping yielding 76 (69%); the second an additional 22 (20%); and the third another 4 (4%). These data are very similar to those documented for *Neisseria gonorrhoeae*. They clearly demonstrate that the use of a single swab underestimates the prevalence of chlamydial infection.

Cytologic methods

Cytologic identification of chlamydial infections—the only method available in the period 1909 to 1957—is an examination of epithelial cell scrapings (e.g. conjunctival, cervical, urethral) on the stained smear. A modified Giemsa stain is most often used, although Wright's and other standard tissue stains can be used. Infection is identified by visualizing characteristic intracytoplasmic inclusions. Alternatively, cell scrapings can be examined using FA stains (Figure 46.3).

The advantage of cytologic examination is clearly the simplicity of the process, particularly if light microscopy is used. The disadvantage is the poor sensitivity for diagnosing chlamydial infection. The sensitivity of cytologic methods in identifying chlamydial adult conjunctivitis is 45% for Giemsa and 85% for FA. In tests for cervical infection, the two stains have sensitivities of only 40% and 65%, respectively, and for urethral infection, 15% and 60%. Moreover, these upper levels of sensitivity can only be obtained with good specimens (many epithelial cells) and an experienced observer. Standard cytology is of little practical value as a diagnostic aid for genital chlamydial infection.

Antigen detection

The four principal methods of chlamydial antigen detection are: (Table 46.2)

(1) FA examination of a direct smear;
(2) enzyme immunoassay (EIA);
(3) DNA probes; and
(4) polymerase chain reaction (PCR).

Commercially available non-culture methods of detecting *C. trachomatis* in general have sensitivities

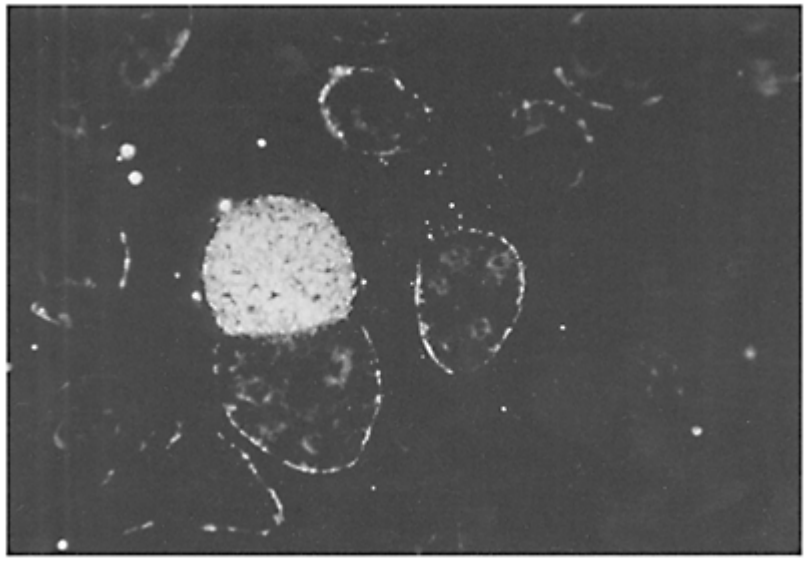

Figure 46.3 Fluorescent antibody stains for *Chlamydia trachomatis*

greater than 70% and specificities greater than 95% compared to culture. Continued revision of these tests takes place even after they become available commercially. Consequently, initial published data on efficacy may be outdated, so the most recent reference should be used.

Fluorescent antibody

Compared with culture, the sensitivity of the directsmear FA test is greater than or equal to 90% in most published studies, and the specificity is greater than or equal to 98%. The positive predictive value of this test has ranged from approximately 80% in populations with a chlamydia prevalence of 10% to 95% in populations with a chlamydia prevalence of 30%. Lower sensitivities and specificities are often encountered in situations in which specimens are less than optimal or individuals reading the slides are relatively inexperienced. In these instances, assessment of the proficiency of laboratory techniques is essential.

Enzyme immunoassay

The EIA test measures antigen-antibody reactions through an enzyme-linked immunoabsorbent assay (ELISA) and requires a spectrophotometer. Processing time for specimens is approximately four hours.

Questions continue to be raised about the reliability of EIAs for *C. trachomatis*. The sensitivity of the test has varied from 67–90%, the specificity from 92–97%, and the positive predictive value from 32–87%, depending on the population studied. Much of

the observed disparity has been attributed to variable sensitivities of the tissue culture systems against which the EIA has been compared.

Table 46.2 Test systems selection for identification of *Chlamydia trachomatis*

Clinical situation	***Test procedure of choice***
Low-prevalence screening	DNA hybridization probe (ultimately amplified DNA probe technologies)
Sexually transmitted disease clinic	DNA hybridization probe (ultimately amplified DNA probe technologies) PCR
Sexual assault/abuse	Culture only method recommended*
Test-of-cure	
if <3 weeks	Post therapy culture
if >3 weeks	Post therapy culture or DNA hybridization probe

*If culture obtained within 48 hours after exposure, it is recommended that a second culture be obtained in two weeks in the absence of preventative therapy.

Probes

The use of DNA probes have been recently introduced for the diagnosis of chlamydial infection. Nucleic acid hybridization tests are based on the ability of complementary nucleic acid strands to specifically align and associate to form stable double-stranded complexes. The probe uses a chemoluminescent labeled, single stranded DNA probe that is complementary to the ribosomal RNA of the target organism. After the ribosomal RNA is released from the organism, the labeled DNA probe combines with the target organism's ribosomal RNA to form a stable DNA:RNA hybrid. The labeled DNA:RNA hybrid is separated from the nonhybridized probe and measured. The principal advantage of the DNA probes is the ability to concomitantly screen for *Neisseria gonorrhoeae*. The benefits derived from the detection of additional positive specimens for *N. gonorrhoeae* outweighs the additional cost over the more standard diagnostic techniques.

Polymerase chain reaction

The PCR or ligase chain reaction (LCR) or transcription-mediated amplification (TMA) test have extremely high sensitivities and specificities when compared with culture PCR test and can be used for not only organismal detection, but also serotyping of infecting serovars. One of the great advantages of techniques such as PCR is the ability to detect *C. trachomatis* DNA in urine samples.

Non-invasive specimen collections

Urine as a test vehicle for chlamydia detection

Because of the frequency of concomitant urethral colonization, copies of target DNA within a urine sample can be detected by nucleic acid amplification tests. Lee *et al.* demonstrated that LCR testing on urine obtained from women gave sensitivities and specificities of 95.7% and 100% respectively.

The urine to be tested should ideally meet the following criteria:

(1) the first 10 to 25 ml of urine voided;
(2) collected between 1 and 2 hours after previous urination; and
(3) stored at 2 to 8ºC prior to testing.

Vaginal introitus sampling

DNA, PCR or LCR testing of vaginal introitus specimens may provide an incidence of identification reasonably comparable to cervical sampling. Vaginal introitus specimens can be self-collected.

Specimen collection for culture

Endocervical

A dacron cotton, calcium agliate-type swab should be used to obtain specimens from the endocervix. Swabs with wooden shafts may cause toxicity to cell cultures. The swab should be inserted past the squamocolumn juncture about 2 cm and rotated for 15 to 30 seconds. If a Papanicolaou smear is to be collected, it should be done so before endocervical sampling. The pooling of a urethral swab specimen with endocervical swab specimens increases culture sensitivity. The likelihood of isolation is optimized if specimens are refrigerated immediately after collection and kept at 2 to 8ºC until transported to a testing facility. If greater than 48 hours will elapse between collection and specimen processing, freezing at −70ºC is an option. Freezing specimens at −70ºC is associated with a 20–30% loss of viability. Freezing of specimens at −20°C is to be avoided.

Specimen collection for non-culture tests

Once vaginal secretions are removed, collection of specimens for commercially licensed non-culture test should be performed as instructions.

Serology

Currently chlamydia serology has little value in routine clinical management and basically remains a research tool. Although some serologic tests are commercially available, they have not been shown to be useful in routine diagnosis.

There are two standard methods—complement fixation and microimmunofluorescence (MIF). ELISA tests have been developed, but none are recommended for wide use. The only valid clinical uses of serologic tests are in infant pneumonia, where specific immunoglobulin M (IgM) MIF serology, when available, is the diagnostic test of choice; and in occasional cases of suspected lymphogranuloma venereum (LGV). The difficulties in preparing the antigen and conducting the test restrict the use of the test to a limited number of research laboratories.

Proficiency in specimen collection and transport is paramount to accuracy in diagnostic testing for *C. trachomatis*. Both the sensitivity and the specificity of diagnostic tests for *C. trachomatis* are directly related to the adequacy of specimen collection. The choice of test system for the identification of *C. trachomatis* is a partial function of availability and clinical setting (Table 46.2).

CONCURRENT GONOCOCCAL AND CHLAMYDIAL INFECTIONS

Depending upon on the study population and methodology used, 20–40% of women with documented endocervical gonorrhea are concomitantly infected with *C. trachomatis*. Asymptomatic women with lower tract chlamydial infection have a low rate of co-infection. Most estimates have been between 1 and 5%. Women with one STD warrant study to exclude others.

TEST OF CURE

Historically, routine test of cure during the immediate post-therapy period is not recommended. The CDC states that patients do not need to be retested for chlamydia after completing treatment with doxycycline or azithromycin unless symptoms persist or reinfection is suspected because these therapies, if taken, are highly efficacious. A test of cure should be considered 3 weeks after completion of treatment with erythromycin. With non-cultured tests, residual chlamydial antigen and nucleic acid in the absence of viable organisms may result in a positive test. Such a positive result can be misinterpreted as a treatment failure. False-positive tests can occur up to three weeks after doxycycline therapy.

Since the prevalence of infection in test of cure is very low, tests with the highest positive predictive value, e.g. culture, are advocated. After three weeks, nucleic acid amplification tests, such as PCR and LCR, which have high predictive values can be utilized. The use of combined *Neisseria gonorrheae/Chlamydia trachomatis* for test of cure is an uneconomical use of technology when culture is available. Use of DNA probe

as a test of cure is warranted only if both organisms were initially identified or no other means of documenting eradication is available.

Table 46.3 CDC recommended regimens for *Chlamydia trachomatis* (2002)

Adult recommended regimens
Azithromycin 1 g orally in a single dose*
or
Doxycycline 100 mg orally twice a day for 7 days*
Alternative regimens
Erythromycin base 500 mg orally 4 times a day for 7 days
or
Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days
or
Ofloxacin 300 mg orally twice a day for 7 days
or
Levofloxacin 500 mg orally for 7 days
Recommended regimen for pregnant women
Amoxicillin 500 mg orally 3 times daily for 7 days**
or
Erythromycin base 500 mg orally 4 times daily for 7 days
Alternative regimens for pregnant women
Erythromycin base 250 mg orally 4 times daily for 14 days
or
Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days
or
Erythromycin ethylsuccinate 400 mg orally 4 times daily for 14 days
or
Azithromycin 1 g orally, a single dose

*While azithromycin and doxycycline have shown equal efficacy in studies to date, these clinical trials have primarily been done in populations where follow-up has been strongly encouraged and compliance with a 7 day regimen has been good.
**The chapter author strongly disagrees with the recommendation for amoxicillin; the penicillin will push chlamydia into latency but some isolates may regain their infectious form in time.

ADULT THERAPY

Non-pregnant women

The therapies of choice for non-gravid women with endocervical or urethral infection are (Table 46.3): azithromycin 1 g orally in a single dose; or doxycycline hyclate, 100 mg, by mouth 2 times a day for 7 days.

Alternate regimens available for patients for whom tetracyclines are contraindicated or not tolerated are: erythromycin base or stearate, 500 mg, by mouth 4 times a day for 7 days; or erythromycin ethylsuccinate, 800 mg, by mouth 4 times a day for 7 days; or ofloxacin 300 mg orally 2 times a day for 7 days; or levofloxacin 500 mg orally for 7 days.

Doxycycline, ofloxacin and levofloxacin are contraindicated in pregnant and lactating women.

Infected patients with concomitant HIV should receive the same treatment regimen as those who are HIV-negative.

In populations with erratic health-seeking behavior, poor drug compliance, or little follow-up, azithromycin may be more cost-effective as it provides single-dose, directly observed therapy. Azithromycin is approved for use in persons ≤15 years of age. Doxycycline has a longer history of extensive use, and the advantage of low cost. Erythromycin is less efficacious than azithromycin or doxycycline and gastrointestinal side effects frequently discourage patients from complying with this regimen. Ofloxacin is similar in efficacy to doxcycline and azithromycin, but is more expensive and offers no advantage in dosing. Ofloxacin is the only quinolone with proven efficacy against chlamydial infection.

To maximize compliance with recommended therapies, medications for chlamydial infections should be dispensed on site. To minimize further transmission of infection, patients treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single dose therapy or until completion of a 7 day regimen. Patients should also be instructed to abstain from sexual intercourse until all of their partners are cured to minimize the risk of infection.

Pregnant women

The teratogenic and/or embryopathic effects of the tetracycline and fluoroquinolones preclude drug utilization in pregnancy.

Schachter *et al.* treated 65 gravidas with erythromycin ethylsuccinate (400 mg four times a day for seven days). Five of the 10 women who had gastrointestinal disturbances discontinued therapy. Of the 60 women and 59 infants who completed the entire protocol, 55 (92%) of the women had negative cultures for chlamydia at follow-up. The introduction of azithromycin one gram bolus dose has significantly impacted on chlamydia therapy in pregnancy. Despite its higher cost, achieving patient compliance and effective therapy with a single administration clearly overshadows the consequences of failed therapy.

Because the chlamydia cell wall is different from bacteria, beta-lactam antibiotics such as penicillins lack bacterial activity *in vitro* against these microorganisms. Nevertheless,

the penicillins appear to drive *Chlamydia* into latency from which some will ultimately escape in time. The cephalosporins and aminoglycosides have no effect on *C. trachomatis* whatsoever.

Management of sex partners

Patients should be instructed to refer their sex partners for evaluation, testing and treatment. Because exposure intervals have received limited evaluation, the following recommendations are somewhat arbitrary Sex partners whose last sexual contact with the index patient was within 60 days of onset of the index partner's symptoms or of diagnosis, which ever is later, should be evaluated, tested, and treated.

PREVENTION

Sexually active women aged 18–25 should be screened for chlamydial infection annually. Similarly, any women with a new sex partner or multiple sex partners should be screened as frequently as warranted by her risk factors. Women who have had chlamydial infection should be rescreened 3–4 months after treatment.

All pregnant women should be screened for chlamydial infection in the first trimester or at the first clinic visit. Serious consideration should be given to rescreening women with high risk factors again at 36 weeks.

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47
Chlamydia trachomatis lymphogranuloma venereum (L) strains

FEMALE GENITAL TRACT INVOLVEMENT

Lymphogranuloma venereum (LGV), a rare disease in the United States, is caused by the invasive serovars L1, L2, or L3 of *Chlamydia trachomatis*. Although its distribution is world-wide, LGV is more common in tropical and semitropical climates. The mode of transmission is believed to be through coitus or intimate physical contact. A number of small endemic foci have been traced to a specific prostitute. The disease may also be disseminated by close non-sexual contact as well as by autoinoculation. Disease has occurred in laboratory workers.

Classically, if the primary lesion occurs on the external genitalia, LGV presents as a transient herpetiform lesion. Although a grippe-like syndrome characterized by fever, malaise, headache, and anorexia may occur, it is rarely the chief presenting complaint in patients with LGV. Fever is present in over 50% of the cases and tends to correlate primarily with the severity of illness. Patients usually seek medical care because of acute inflammatory changes within lymph nodes or bloody proctocolitis. Manifestations of neglected disease are either consequences of lymphatic blockage draining the primary infection (elephantiasis) or scar tissue.

The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is most commonly unilateral. Women and homosexually active men may have proctocolitis or inflammatory involvement of perirectal or perianal lymphatic tissues resulting in fistulas and strictures.

Lymphogranuloma venereum in its initial presentation may occur as one of two syndromes—either inguinal or genitorectal.

Inguinal syndrome

The initial genital lesion which develops varies from a slight erosion to a small cutaneous herpetiform lesion. It may either disappear or develop into an ulcer. The lesion is painless and only slightly tender to palpation. It exhibits ill-defined shallow margins and a fibrogranular base. The fourchette, urethral meatus, and medial surface of the labia are the usual sites of primary lesions. Clinical recognition of infection at this stage is the exception, not the rule. When multiple lesions are present, the adjacent labia or clitoris is often edematous. In the absence of secondary infection, most of the lesions will have healed prior to the onset of lymph node enlargement.

More than 50% of infected patients manifest no clinical symptoms. While most male patients develop inguinal adenopathy during the course of disease, this manifestation is relatively unusual in females (Table 47.1). The adenopathy may vary from shoddy nodes

to fluctuant masses often associated with draining sinuses. Involvement of the inguinal and femoral lymph nodes may result in masses on either side of the inguinal ligament (so-called groove sign). Lymph node involvement is indicative of lymphatic drainage from the primary lesions, and consequently unilateral adenopathy is not uncommon. The regional glands draining the primary site of infection, particularly in the male, enlarge dramatically and may appear as a series of buboes. Sixty percent of the buboes rupture, discharging a copious watery to purulent granular exudate.

The early histologic appearance of lymph nodes is that of diffuse reticular and lymphocytic hyperplasia.

Table 47.1 Differential diagnosis of inguinal adenopathy associated with a presumed venereal disease

Disease	*Genital lesion*	*Nodal involvement*	*Cutaneous lesions*
Granuloma inguinale	Extensive in males, less evident in females	Involvement of lymph nodes; draining cutaneous sinuses; late in the course of the disease; nodes become tender	Primary skin infection with superficial ulceration
Lymphogranuloma venereum	Occurs but is extremely transient in nature	Bilateral node involvement is determined by site of primary lesion	Multiple sinus tracts draining a thick, creamy exudate
Chancroid	Usually present	Primarily unilateral with limited involvement of lymph nodes	Acute, with crater-like slough
Genital tuberculosis	None	Bilateral inguinal adenopathy	Pleomorphic, often with sinus tract draining scanty thick exudate
Syphilis	Usually present	Bilateral; firm, rubbery nodes	Protean in its clinical manifestations

In the more advanced lesion, macrophages appear in significant numbers prior to the development of central necrosis. The macrophages assume a palisade-like arrangement around the central focus of necrotic cellular debris. Plasmacytosis is one of the important supplementary criteria in the histologic diagnosis of LGV. Healing is associated with fibroblastic proliferation and (ultimately) with the replacement of the diseased foci by fibrous connective tissue. Extensive cutaneous scarring may suggest the diagnosis in a patient seen for the first time late in the course of the disease.

If urethral involvement occurs, it exhibits the same sequential pattern—first ulceration and then destructive lesions with healing by fibrosis. Patients with partial urethral destruction may remain continent as long as the distal portion of the urethra is intact. Partial obstruction may cause difficulty in voiding. The resultant symptoms are those of urethral obstruction. Complete urethral destruction represents a difficult therapeutic challenge, necessitating surgical reconstruction.

Genitorectal syndrome

The second syndrome, genitorectal, accounts for 25% of the cases seen in the early stage, and occurs predominantly in women. In the male, lymphatic drainage from the initial lesion is primarily to the inguinal lymph nodes. In the female, the perirectal and pelvic lymph nodes are the primary sites of drainage.

Rectal involvement occurs by contiguous spread from the perirectal lymph nodes. Initially proctocolitis develops, characterized by mucopurulent discharge and bloody diarrhea. Secondary bacterial infection of the ulcerated lesions and adjacent mucosa contributes significantly to the disease process. The proctitis is most severe at the anorectal ring. The regional mucosa is edematous, hemorrhagic, and friable. Neither adenopathy nor systemic signs and symptoms comparable to those attending the inguinal syndrome are commonly observed with this form of the disease. If treated with antibiotic agents and a low-residue diet, this stage of the disease can be cured, leaving no residual stigmata. No sharp clinical demarcation exists between late-stage proctitis and early stricture formation. The perirectal and rectal tissues become secondarily involved by contiguous spread; consequently, with healing, induration of the lower third of the posterior vagina and scarring of the rectovaginal septum are frequent findings. Extensive disease may result in strictures as far as the rectosigmoid junction.

Rectal stricture may then cause additional symptoms, namely, those of chronic obstruction of the distal colon. Occasionally, the infection culminates in intestinal obstruction sufficiently acute to necessitate colostomy. Once significant fibrosis with stricture formation has occurred, surgical incision of the stricture is the prime therapeutic modality.

A physiologically significant rectal stricture is important in the pathogenesis of a rectovaginal fistula. Almost invariably, rectovaginal fistulas occur in patients with stricture. The site of the fistula is fairly constant: at or below the level of the stricture in the midline about 2.54 to 3.81cm from the fourchette.

Lesions in the late stages may not exhibit active inflammation or ulceration. There is no sure way of distinguishing burned-out cases from those that are still active and for which systemic therapy should be initiated prior to any attempt at repair or plastic procedures.

Laboratory results, with the exception of complement fixation or microimmunofluorescent tests for LGV, are inconclusive. Abnormalities in the white blood cell count include mild to marked leukocytosis with a relative lymphocytosis. Biologically false-positive serologic tests for syphilis not infrequently occur. In longstanding disease, the albumin-globulin ratio is inverted.

Lymphogranuloma venereum and vulvar carcinoma

Lymphogranuloma venereum is often cited as a predisposing factor in vulvar carcinoma. This circumstantial association is based largely on the coexistence of the two diseases and on the observation that with a history of LGV, cancer of the vulva occurs at a significantly earlier age. If vulvar carcinoma develops in a patient with previous or concomitant LGV, the latter disorder appears to influence the natural history of the disease. Metastases through the lymphatics appear to be delayed, presumably because of inflammatory or postinflammatory alterations of the lymphatics.

Lymphogranuloma venereum in pregnancy

Lymphogranuloma venereum may complicate pregnancy as a consequence of the inflammatory lesions and subsequent scar tissue formation involving the vagina and rectum, which may impede normal vaginal delivery.

The disease process may result in vulvar elephantiasis esthiomene and produce a soft tissue outlet dystocia. In this circumstance, the management of delivery is similar to that in other types of soft tissue outlet dystocia.

A significant impediment to the descent of the presenting part as a consequence of extensive fibrosis is seen in the chronic stages of the disease. The obstruction reflects reparative fibrosis which follows the retrograde spread of infection into both the bases of the broad ligament and the soft tissues of the pelvic wall. Rupture of the rectum or uterus is a potentially lethal complication of vaginal delivery in such cases. In rectal rupture, the pelvic portion, if fixed to the vagina, is torn away from the segment above the pouch of Douglas, where it is adherent to the sacrum by scar tissue. Kaiser and King, in their compendium on the subject, recommend that the mode of delivery be based on the evaluation of the soft tissues of the pelvis prior to delivery. The extent of involvement can be ascertained under anesthesia in terms of:

(1) the presence of rectal stricture;
(2) fixation in the region of the pouch of Douglas;
(3) adnexal thickening; and
(4) the presence of fistula formation.

When a trial of labor appears to be justified, it should be borne in mind that failure of descent of the presenting part is an indication for cesarean section rather than trial of forceps or version, regardless of the degree of cervical dilation. Version and extraction or any form of forceps delivery is contraindicated. If vaginal delivery is achieved, the patient must be carefully monitored for signs of rectal or uterine rupture. Postpartum shock, associated with lower abdominal pain and peritoneal irritation, necessitates immediate laparotomy following rapid expansion of the intravascular compartment and antibiotic therapy.

DIAGNOSIS

Disease in women is difficult to diagnose. The female patient is more likely to present with the genitorectal than with the inguinal syndrome or with inguinal adenopathy in a subclinical form.

With primary infection she may complain of a small boil on the vagina or a slight discharge or irritation. Most often the small shallow red ulcers with flat margins due to LGV escape clinical detection.

The second stage of disease, in which adenitis predominates, may pass unnoticed until a late phase in which fibrosis or tissue destruction has developed. Symptoms of disease are the result of destruction and secondary fibrosis involving the rectum, urethra, or lymphatic drainage of the labia. The patient may complain of urinary or fecal incontinence, or both, diarrhea, dyspareunia, or discomfort due to swelling of the vulva (vulvar elephantiasis). Rectal lesions are likely to draw the attention of gynecologists

when either a rectovaginal fistula develops or repeated straining at stool leads to uterine prolapse. Lymphogranuloma venereum must be considered in the differential diagnosis of any fistulous tract involving the perineum.

The chlamydial complement fixation test is used to confirm exposure to *C. trachomatis*. Titers equal to or greater than 1:64 are regularly present in the serum of women with LGV.

Initially developed for serotyping strains of *C. trachomatis*, the microimmunofluoresence test effectively measures antibody response to the selective serotypes in its pool. It is of considerable value in documenting infection due to L serovars. Serologic confirmation of prior and/or concurrent antigenic experience with chlamydia organisms, coupled with a characteristic disease clustering, makes the diagnosis of LGV.

THERAPY

Therapy is directed not only at curing infection/disease, but also preventing or limiting healing complications of scarring and chronic lymphatic blockage. In nonpregnant women, doxcycline is the preferred treatment (100 mg orally 2 times a day for 21 days). Doxcycline is contraindicated in pregnant and lactating women. An erythromycin regimen is preferred when clinical ambiguity exist between LGV and chancroid *(Haemophilus ducreyi)*.

Erythromycin is the drug of choice in pregnant and lactating women (500 mg orally 4 times a day for 21 days). The activity of azithromycin against *C. trachomatis* suggests that it may be effective in multiple doses over 2–3 weeks but substantial clinical data on its use are lacking.

Aspiration of fluctuant nodes can be implemented as a therapeutic adjunct in adenitis. Aspiration of suppurative nodes in lieu of spontaneous rupture has been advocated and appears to be free of significant complications. Aspiration is best achieved with a number 20 needle, inserting it through adjacent non-involved skin rather than aspirating the lesion directly through skin overlying the node.

A patient with significant disease must be monitored for possible development of vulvar carcinoma. Biopsy of any suspicious lesion is mandatory.

Women with both LGV and HIV infection should receive the same treatment regimens as those who are not HIV-positive. Prolonged therapy may be required to achieve resolution of disease.

Management of sex partners

Persons who have had sexual contact with a patient who has LGV within 30 days before onset of the patient’s symptoms should be examined, tested for urethral chlamydial infection, and treated.

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48
Mycoplasma

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The mycoplasmas are small (0.2–0.3 mm) membrane-bound pleomorphic, free living procaryotes. They are the smallest organisms capable of independent self-replication. They belong to the class of Mollicutes which is a taxon that contains small procaryotic organisms bounded by a single cell membrane. Mollicutes have no known relationship to bacteria, but because of their filamentous, star shape, or spherical appearance, they can be confused with cell wall deficient L-forms.

Mycoplasmas do not stain with Gram's reagent. They stain poorly with Giemsa stain. Colonies are recognized on special solid media either by a characteristic 'fried egg' configuration or by the formation of small golden spherules. The organisms are fastidious in their growth requirements. It is necessary to provide them with enriched media containing peptone, yeast extract, and serum. These materials provide a source for urea, nucleic acids and cholesterol. Members of the class can be identified by their ability to hydrolyze urea *(Ureaplasma urealyticum),* utilize arginine (*Mycoplasma hominis* and *Mycoplasma fermentans*), or ferment glucose (*M. fermentans* and *M. genitalium*).

Ureaplasma urealyticum is unique among bacteria in its requirement for urea even when inoculated into complex media.

The absence of a cell wall makes mycoplasmas insensitive to penicillin and other antibiotics whose action depend on interference with cell wall synthesis.

GENITAL STRAINS

Four strains can be recovered from the genital tract: *Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma fermentans,* and *Mycoplasma genitalium*.

M. hominis and *U. urealyticum* are recovered frequently from the cervix and vagina of sexually experienced women. Carriage of *M. hominis* and *U. urealyticum* is so common in women that it has been considered normal flora by some. Both organisms have been isolated from blood postparum and after abortion. Such isolations are sometimes associated with a low-grade fever.

Like other sexually transmitted organisms, the probability of recovery from the lower genital tract is directly related to the number of sexual partners either the patient or her partner are exposed to.

The presence of mycoplasmas in the lower genital tract of women is not necessarily associated with clinical evidence of infection.

LABORATORY DIAGNOSIS

The proper handling of specimens is critical for the recovery of these fastidious microorganisms. Specimens taken on swabs should be received in the laboratory within an hour of collection. Plastic shafted swabs are preferable to wooden ones since they are less likely to contain toxic chemicals that may interfere with optimum growth. Because the microorganisms are in a natural environment, specimens such as semen or urine can be kept for several hours following collection prior to culturing. Two specimens from each patient are recommended in order to ensure the best possible chance of isolation. A cervical swab and urine from the female, semen, urethral swab, and urine from the male are the most readily available, involve the least discomfort, and at the same time yield reproducible information as to the presence of *U. urealyticum* and *M. hominis*.

If the specimens are to be mailed, immediate freezing in dry ice is essential, followed by shipping in dry ice. Freezing results in a loss of microorganisms and is not recommended unless absolutely necessary. There may be a loss of at least two logs in the colony count when samples are frozen and subsequently defrosted for culture.

Considerable experience is necessary for isolation. A solid agar, Shepard's A7 and a broth medium are inoculated simultaneously. Both media are observed daily. The broth is observed for a color change, from yellow to pink. This change indicates that urease, characteristic of *U. urealyticum*, is present. The solid medium demonstrates the presence of actual colonies. The colonies are very small and usually cannot be visualized by the naked eye. Under the low power of the microscope, *U. urealyticum* appear as dark brown, accretion colonies. Classical mycoplasmas appear as almost colorless, film-like colonies with obvious central cores. The classical mycoplasmas, unlike bacterial colonies, accept the Dienes' stain.

No further identification of *U. urealyticum* is required beyond demonstration of the presence of urease and the typical colonial morphology on A7 agar. *Mycoplasma hominis* however, requires further identification. The standard means of identification is the use of known antisera for growth inhibition of a subculture of the original isolate.

Specimens other than genital swabs, semen, and urine have been found positive for the genital mycoplasmas. Isolations of *U. urealyticum* have been made from the placenta, amniotic fluid, and the nasopharynx of neonates and adults, and from the lungs of infants dying in the perinatal period. *M. hominis* has also been isolated from the lungs of infants dying in the perinatal period, the nasopharynx of neonates and adults, and most recently, from the brain abscess of a neonate, and an infected knee joint following total knee replacement.

Because of the observation that tetracycline-resistant strains of *U. urealyticum* and *M. hominis* make up 10–15% of patient isolates, a simple, direct, broth-disk method for antibiotic susceptibility testing was developed by Kundsin *et al.* The test utilizes urine sediment as the inoculum and impregnated paper disks as the source of antibiotic. Antibiotic levels are used which approximate attainable serum levels. Combinations of antibiotics can be tested in this fashion.

GYNECOLOGICAL INFECTION

Mycoplasma hominis and *U. urealyticum* have been isolated from both the lower and upper genital tract of women with classical symptoms of pelvic inflammatory disease (PID). In 1937, Dienes and Edsall isolated mycoplasma in pure culture from a Bartholin abscess. In 1954, Shephard reported the recovery of *U. urealyticum* from men with non-gonococcal urethritis. Since then Kundsin *et al.* have demonstrated that there is a female counterpart to non-specific urethritis in males. Kundsin demonstrated that 80% of women with symptoms of genitourinary infection attending the genital infectious disease clinic at Brigham and Women's Hospital had *U. urealyticum* in their urine as opposed to 2% of nuns in a teaching order in Boston.

Mardh *et al.* have reported isolation of mycoplasmas from the fallopian tubes of patients with a diagnosis of salpingitis verified by laparoscopy. Mardh and Westrom went on further to report that in no cases where there were normal tubes seen through the laparoscope were mycoplasmas isolated from the pouch of Douglas. Others, however, have reported the recovery of mycoplasmas from these areas in some patients without laparoscopic evidence of salpingitis. Other investigators have reported the presence of specific hemagglutination inhibition (HAI) antibodies in patients with acute salpingitis. All patients with HAI antibodies had *M. hominis* in the genital tract and over half of those patients had a fourfold or greater rise in titer.

The recovery of mycoplasmas and ureaplasmas in pure culture from infected fallopian tubes, the demonstration of elevated IgM specific for *M. hominis* in patients with acute salpingitis, and the correlation of indirect hemagglutination antibodies against *M. hominis* with the isolation of *M. hominis* in patients with salpingitis, is strong evidence that mycoplasmas are pathogenic in at least a percentage of patients with salpingitis.

The literature on mycoplasmas and infertility is obviously controversial. *M. hominis* and *U. urealyticum* are reported to be cultured more frequently from women attending infertility clinics, particularly if tubal or cervical abnormalities are detected or if there is an abnormal vaginal discharge. In addition, subtle endometrial changes have been described in as many as 55% of patients with urine cultures positive for *U. urealyticum.* However, double-blind studies have not yet demonstrated a relationship between the presence of mycoplasmas in the lower genital tract and secondary infertility. Although *M. hominis* and *U. urealyticum* have been demonstrated to be capable of attaching to human spermatozoa in infertile patients, the mechanism for infertility presumably caused by the mycoplasmas has not been established. Experiments carried out with *U. urealyticum* serotype 4 suggest the production of diffusible, relatively heat-stable factors responsible for inhibition of sperm penetration of hamster eggs. Since the effects on sperm may be delayed, it is possible that for postcoital tests to be valid they should be performed after eight hours, even if excellent results are obtained at two hours.

Gump, Gibson and Ashikaya presented a study of 205 couples with infertility in whom ovulatory dysfunction was ruled out. The results indicated that in the women studied, isolation of *M. hominis* was more common in patients with a history of PID. However, no relationship could be established between positive cultures and hysterosalpingographic or laparoscopic evidence of previous tubal infection. They could not establish a relationship between the presence of mycoplasmas, and cervical inflammation or postcoital testing. Their conclusion was that, in their series, no association between the presence of genital

mycoplasmas and infertility could be demonstrated. They, however, did not do an eight hour postcoital test. In addition, they used wooden handles on their cotton tipped applicators for sample collection, they did not collect samples from urine, and some of their cultures were obtained from frozen endometrium that was thawed.

Another study of infertile women by Horne and Kundsin found that of 99 consecutive patients, 64 (65%) had genital mycoplasmas. They also noted that antibodies to *Chlamydia trachomatis* were significantly associated with the presence of genital mycoplasmas. Of 23 patients with elevated antibody titers to *C. trachomatis*, 20 (87%) had genital mycoplasmas. Of 76 patients with no *C. trachomatis* antibody titers, 44 (58%) had genital mycoplasmas. This was a statistically significant difference (chi square 6.52, p=0.01). What this means is that essentially most women with *C. trachomatis* antibody titers also have genital mycoplasmas. The role of each microorganism in infertility must therefore be evaluated. This can only be done if cultures for both genital mycoplasmas and chlamydia antibody titers are obtained from each patient evaluated for infertility and matched with suitable controls.

OBSTETRIC INFECTION

M. hominis is found in association with *U. urealyticum* in the genitourinary tract of approximately 10% to 15% of patients. Both of these mycoplasmas, separately or in combination, have been found in human placentas, and their presence has been significantly associated with perinatal morbidity and mortality. Mycoplasmas can be isolated from approximately 15% of pregnant women during the first trimester and this increases to approximately 20% during the last trimester. More than 11 % of women who have afebrile abortions have mycoplasmas present in their cervix. This number is not significantly different from patients who do not abort. In contrast, if fever is considered, 39% of patients who have febrile spontaneous abortions have *M. hominis* isolated from the cervix and the percentage is even higher if stricter criteria for febrile abortion are applied.

Harwick and co-workers reported mycoplasmemia associated with these infected abortions. This observation demonstrates the invasive potential of mycoplasmas. Their conclusion was that in the febrile cases, mycoplasmas might act as opportunistic microorganisms invading only traumatized or previously infected tissues. But there is also the possibility, of course, that they initiate an infectious process that results in fetal wastage.

U. urealyticum is a common commensal of the urogenital tract of sexually mature humans. While its etiologic significance in many aspects of adverse pregnancy remains controversial, recent evidence indicates that *U. urealyticum* in the absence of other organisms is a cause of chorioamnionitis. Furthermore, ureaplasmal infection of the chorioamnion is significantly associated with premature spontaneous labor and delivery. In at least some cases, it appears to be causal. Present evidence indicates that *U. urealyticum* is a cause of septicemia, meningitis, and pneumonia in newborn infants, particularly those born prematurely. There is strong but not definitive evidence that ureaplasmal infection of the lower respiratory tract can lead to development of chronic lung disease in very low-birthweight infants. Although risk factors for colonization of the

lower genitourinary tract have been identified, little information is available concerning risk factors for intrauterine infection and host immune responses to invasive infection.

Isolation of *U. urealyticum* from the placentas of infants born at the Boston Lying-in Hospital also showed a documented increase in morbidity and mortality for those infants whose placentas harbored this microorganism.

Kundsin and associates have reported a relationship between *U. urealyticum* and infertility as well as with spontaneous abortion and ectopic pregnancy. Another phase of the investigation dealt with diethylstilbestrol (DES)-exposed women having problems of infertility. Cultures from this population of women revealed a high rate of isolation of *U. urealyticum* from the genitourinary tract. Furthermore, the incidence of ectopic pregnancy and spontaneous abortion was significantly higher than that found in non-DES-exposed women. Analysis of the data, however, suggested that pregnancy wastage in DES-exposed women is related more to *U. urealyticum* colonization than to DES exposure *in utero*.

Mycoplasmas have been shown to cause chromosomal alterations in cultured human diploid fibroblasts. Reportedly, they can produce lesions on the short arm of chromosomes 21 and 22. Structural alterations in chromosomes have also been reported in human peripheral lymphocyte cultures infected with *U. urealyticum*. It is suggested that since some strains can induce chromosomal change *in vitro,* it is possible that these organisms can also produce chromosomal alterations in the zygote and be responsible for some cases of spontaneous abortion associated with lower genital tract infections with mycoplasmas.

Several studies have demonstrated that genital mycoplasmas, especially the strains of *U. urealyticum,* are isolated more frequently in the lower genital tract of women who deliver placentas with histologic evidence of chorioamnionitis when they are compared with the placentas of women who have no manifestations of inflammation. Most of the studies correlating chorioamnionitis with the presence of mycoplasmas have had poor controls and lack the results of serologic antibodies in the mother and the neonate to demonstrate an adverse effect of colonization by these organisms.

The literature therefore does not support unequivocally the theory that a direct relationship exists between sexual activity in pregnancy and isolation of mycoplasmas from the lower genital tract of women who develop chorioamnionitis.

An association between *M. hominis* in the genital tract and low birthweight has been postulated. A report by McCormack *et al.* indicated that patients treated 4 times daily with erythromycin for 6 weeks in a randomized double-blind study gave birth to infants with heavier mean birthweights when compared with infants born to placebo treated women. Erythromycin treatment had no effect when administered in the second trimester. In contrast, women whose treatment with erythromycin was initiated in the third trimester had babies with heavier mean birthweight than the babies born to the placebo treated women. The incidence of infants weighing 2500 grams or less was 3% while women treated with placebo gave birth to babies at or below this weight 12% of the time. This difference was statistically significant. The data suggested that treatment with erythromycin during the third trimester prevented low birthweight in mycoplasma-colonized pregnant women. It was not certain, however, whether the erythromycin effect was also due to an action on *U. urealyticum.*

Postpartum fever has been associated with *M. hominis* infection confirmed by blood culture and with a significant elevation in antibody titer. The possibility that mycoplasmas can be responsible for postpartum morbidity should always be considered in postpartum patients with cryptogenic fever. This is especially true if there have been no abnormalities during the labor or any operative intervention.

Mycoplasmas are ubiquitous in the genitourinary tract of pregnant women. Local changes in the genital tract associated with the pregnant state may favor recovery of *U. urealyticum* and *M. hominis* from the genital tract. It is almost certain that mycoplasmas are at least synergistic organisms in the development of fever in some parturient and postpartum females. It is most likely that they do represent in some cases primary true pathogens involved in the infectious process.

In summary, both *U. urealyticum* and *M. hominis* have been incriminated in sexually transmissible disease in adults, in infertility and reproductive wastage, in postpartum and postabortal maternal infection, and in neonatal morbidity and mortality. Definitive proof is still lacking.

The controversy regarding the significance of *U. urealyticum* and *M. hominis* infections demands that any studies on the association of these microorganisms with human infection be done by competent individuals thoroughly familiar with appropriate methodology for securing specimens, transporting them, culturing them on appropriate media, and with identification of isolates.

If mycoplasmas are shown unequivocally to be related to reproductive morbidity and mortality, the resolution of the health problems caused by these microorganisms will depend on the application of reliable techniques for isolation, identification, and determination of antibiotic susceptibilities of the offending strains. Appropriate and effective therapy will depend on these factors.

THERAPY

M. hominis is susceptable to the tetracyclines, but quickly develops resistance. It responds to clindamycin, but is resistant to erythromycin. *U. urealyticum* can be treated with erythromycin.

Simple carriage of these organisms in the vagina does not warrant therapy

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Borrelia recurrentis (relapsing fever)

Borrelia is a genus of spirochetes belonging to the Spirochaetoceae. Morphologically, the typical organism is composed of five to ten loosely wound, irregular coils measuring 10–35μ in length and 0.3–0.5μ in width. Although susceptible to desiccation and to many chemical agents, the organisms are able to survive in citrated blood for as long as three months at 2–3°C. Disease caused by these spirochetes may be divided into:

(1) an epidemic form in which the body louse, *Pediculus humanus corporis,* is usually the principal vector; and
(2) an endemic form in which infection is mostly transmitted through ticks of the *Ornithodoros* genus.

In the natural life cycle, arthropod infection is acquired when lice feed on a patient during an attack of relapsing fever. Only about 12–17% of lice feeding on patients experiencing an attack of relapsing fever transmit infection. A louse ingests up to 1 mg of blood during a single feed. This meal must contain at least one to two organisms per oil immersion field to be infective. The spirochetes enter the mid-gut of the louse, disappearing therefrom in about one day. A ‘negative phase’ ensues in which borreliae are present as granules which can be distinguished only by fluorescent microscopy. After five to six days, short, corkscrew-like metacyclic forms appear in the coelomic cavity of the louse. Thereafter, the louse is infected for its lifetime.

Since the infection does not involve the parasite’s salivary or coxal glands and the microorganisms are not found within the louse’s gastrointestinal tract or feces, transmission of relapsing fever necessitates the crushing of the lice, permitting coelomic fluid containing borreliae to contaminate the site of the bite. It is believed that the organisms are capable of penetrating either very small abrasions or, if ingested, intact intestinal mucosa. In contrast, the host-parasite relationship between *Borrelia* and its endemic arthropod vector, the tick, is far more sophisticated. Spirochetes persist in saliva, coxal gland fluid, and feces, thus facilitating human infection independent of being crushed into the bite lesion. Ticks, in feeding, not only permit saliva to reach open capillary beds, but toward the end of the meal also evacuate the contents of the gut as well as excreting coxal fluid. A single spirochete is sufficient to initiate disease. Spirochetemia which persists for several weeks ultimately results in metastatic infection of the central nervous system, eyes, and visceral organs. *Borrelia burgdorferi* is able to achieve prolongation of its phase of spirochetemia by multiphasic antigenic variation.

Louse-borne disease is usually associated with conditions of overcrowding, poor housing, undernutrition, and lack of sanitation, circumstances that may attend prolonged disaster. On the other hand, tick-borne *Borrelia* infections most often reflect disease in individuals who are newly arrived within an endemic setting.

Although tick- and louse-borne disease induce the same syndrome in man, variations exist in incubation periods, in severity of clinical manifestations, and in recurrences of febrile episodes. In general, louse-borne relapsing fever has a longer incubation period (9–14 days) than that observed with tick-borne *Borrelia*. In both forms of *Borrelia* infection, disease is heralded by chills, fever, nausea, vomiting, myalgia, arthralgia, and photophobia. The temperature may reach 42–43ºC and is almost always significantly elevated. In the louseborne variant, the first episode of unremitting fever lasts 3 to 6 days and is followed by a single less severe episode. Tick-borne relapsing fever is characterized by multiple temperature spikes of 1 to 3 days. The interval between febrile periods ranges from 4 to 14 days.

Tracheobronchitis, meningeal involvement, erythematous macular rashes, and petechiae are not uncommon, particularly with louseborne *Borrelia*. With tick-borne borreliae, severe ophthalmologic and neurologic involvement is characteristic. These manifestations may appear late in the disease and leave permanent sequelae.

The first febrile episode terminates in crisis in which the patient exhibits hyperthermia, shaking chills and hypertension. The crisis is followed by profuse diaphoresis and hypotension. Maternal and fetal death most commonly occur during the crisis or shortly thereafter.

Relapses are contingent on the selection and replication of antigenic variants of the original *Borrelia* strain. Each relapse clinically emulates the preceding episodes, only in a more attenuated form. The pyrexial attacks become shorter and the intercalary periods longer.

For untreated relapsing fever, the eventual eradication of the organisms is contingent on the synthesis of lysins and immobilizins with a sufficiently broad antigenic spectrum to cover all significant antigenic variants.

Therapy *per se* introduces an added risk factor. Up to 90% of patients with louse-borne relapsing fever and 40% of those with tick-borne relapsing fever experience a Jarisch-Herxheimer reaction. Within one to two hours the patient experiences intense shaking chills, elevation of an already elevated temperature and apprehensiveness. In a minority of patients, the reaction is life-threatening.

FEMALE GENITAL TRACT INVOLVEMENT

Pregnant women are at a higher risk of more severe disease and adverse pregnancy outcomes.

Acute infection with either form of relapsing fever may result in adverse effects on the conceptus. Abortion is not an infrequent consequence of an acute attack during gestation. Although most cases are probably secondary to the maternal response to systemic illness, a number of late abortions may be due to direct involvement of the products of conception. It has been clearly demonstrated that, as with *Treponema pallidum*, congenital infection occurs. Whether or not transplacental transmission occurs is not contingent on the severity of maternal infection. Attenuated maternal disease does not preclude fetal involvement. The diagnosis of congenital infection necessitates both the onset of neonatal disease prior to the third day of life and demonstration of spirochetes in peripheral blood smears. Hyperbilirubinemia and evidence of meningoencephalitis

predominate. In necropsy material, the principal pathologic findings involve the central nervous system and the spleen. The meninges are thickened due to predominantly mononuclear cell infiltration. Scattered neutrophils are present in areas of cellular necrobiosis. Macroscopically, the cut surface of the spleen usually reveals scattered yellow miliary lesions that, on histologic examination, are seen to be composed of focal areas of coagulative necrosis. Touch preparations of spleen or meninges, stained with Giemsa's or Wright's stain, or silver impregnation stains of fixed tissue reveal spirochetes with large irregular spirals characteristic of the *Borrelia* genus.

DIAGNOSIS

Definite diagnosis of *Borrelia* is made by demonstration of spirochetes in blood, cerebral spinal fluid or tissues. Blood samples for diagnostic analysis should be obtained with the onset of fever and before its zenith. Once the temperature is declining uninfluenced by antipyretics, visual detection of spirochetes in blood is markedly diminished. Thin and thick smears of blood need to be obtained. Direct identification of spirochetes in blood correlates with approximately 100000 organisms per ml of blood. Centrifugation of the blood and examination of the buffy coat and overlying plasma increases the sensitivity of direct microscopy Spirochetes are found in the same fraction as are platelets.

When the diagnosis of relapsing fever is strongly suspected but the spirochetes have not been directly visualized, inoculation of blood into weanling mice can demonstrate the presence of a *Borrelia* species. Stain smears of tail blood are examined for spirochetes one to four days later. *In vitro* culturing of blood on selected media is an alternative to animal inoculation. These latter techniques are applicable in the latter phase of a febrile episode or between fever spikes.

Borrelia can be stained with most aniline or acid dyes. Dehemoglobinization of slides with 6% acetic acid and 95% ethyl alcohol for 5 seconds, followed by staining

Table 49.1 Advocated antibiotic regimens in the treatment of infection with *Borrelia*

Drug of choice	***Dosage/duration of therapy***	
	Louse borne	***Tick borne***
	Febrile phase	
Penicillin	Procaine penicillin G (800000 units; route of administration: IM/single dose)	3 million units of penicillin G qid;oral/10–14 days
Tetracycline	250 mg followed by another 250 mg in 4 hours; route of administration oral or IV/single dose	500 mg qid; oral/10 days or doxcycline 100 mg bid; oral/10 days
Erythromycin	500 mg oral or IV/single dose	500 mg qid oral/10 days
Alternate beta-lactam antibiotic: ceftriaxone 1 g bid; oral/10–14 days		

with carbol fuchsin for one minute, provides a simple procedure applicable to both thin and thick smears.

An alternative method for demonstrating the organism is prolonged (10- to 12-hour) staining of ethyl alcohol-fixed smears with Wright's stain followed by the application of 1% crystal violet solution for 10–30 seconds.

Serological tests can provide indirect evidence of infection. Because of antigenic variability these tests are not highly specific. Enzyme-linked immunoabsorbent (ELISA) or indirect fluorescent antibody (IFA) tests are of value when acute and convalescent maternal sera are available. For ELISA results to be considered diagnostic, the Western blot assay for Lyme disease and reagin-based and treponema-specific assays for syphilis should be negative. A polymerase chain reaction test can detect *Borrelia* species antigen in blood, cerebrospinal fluid and tissues.

THERAPY

Penicillin and tetracyclines have been the drugs of choice for relapsing fever. The minimal inhibitory concentrations of these antibiotics for *Borrelia* species tends to be less than 0.1µg/ml. Borrelia species are also susceptible to cephalosporins, chloramphenicol, macrolides and vancomycin. In the nulligravid female, the tetracyclines constitute the drug of choice (Table 49.1).

The effectiveness of antibiotic therapy can be monitored by the clearance of spirochetes from the blood. Within eight hours following the administration of an effective antibiotic, spirochetes are no longer demonstrable in the blood.

Drugs that immobilize or destroy borreliae may give rise to a Jarisch-Herxheimer-like reaction, similar to that observed with *Treponema pallidum*. Because of a high probability of a Jarisch-Herxheimer reaction, initial therapy should be done in a controlled environment. A central venous line should be in place as well as means of increasing oxygenation and controlling hyperthermia. Core body temperature can be reduced with tepid water, sponge baths, and/or acetaminophen.

PREVENTION

Personal hygiene and reduction of crowding greatly decreases the potential for louse-borne disease. Once an infestation is identified, delousing of patients and household becomes essential.

When tick exposure occurs on an occasional basis, prophylaxis with tetracycline 500 mg orally qid for two to three days will reduce the risk of infection if taken within two days of exposure.

Antimicrobial drugs can be utilized prophylactically in epidemics. However, the key to prevention of louseborne relapsing fever is the reinforcement of those conditions destructive to lice, notably regular personal hygiene, cleanliness, and disinfection of louse-infested clothing.

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50
Borrelia burgdorferi (Lyme disease)

Lyme disease, first described in 1977, is characterized by a distinctive skin lesion, erythema chronicum migrans (ECM), which starts as a red macule at the site of a tick bite and expands to become an annular erythema with central clearing. Lyme disease is a multisystem disorder that is characterized in various stages by dermatologic, neurologic, cardiac, and rheumatic manifestations. Epidemiologic and serologic studies strongly implicate a newly discovered spirochete, *Borrelia burgdorferi,* as the cause of this disorder. Ticks are the best documented vectors of the spirochete. *Borrelia burgdorferi* has been isolated from *Ixodes dammini,* from *Ixodes pacificus,* and also from *Amblyomma americanum*. The number of cases reported to the CDC (Centers for Disease Control) has increased during the past two years so that Lyme disease is now the most commonly reported tick-borne illness in the United States. Since 1980, reported cases of Lyme disease have occurred in an increasing number of states. Increasing numbers of cases have occurred in three states outside previously recognized endemic areas: Arkansas, North Carolina, and Texas. Isolated, serologically confirmed cases have been acquired in Florida, Georgia, Indiana, Michigan, New Hampshire, Virginia, and Tennessee. However, in all reporting years, more than 70% of all cases were acquired in only seven states: Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin.

CLINICAL MANIFESTATIONS

Cases of Lyme disease are characterized by the presence or the history of the skin lesion (ECM). This lesion is the earliest and most specific observable manifestation of the disorder. ECM that occurs within approximately 30 days after exposure in an endemic area is virtually diagnostic of Lyme disease. If no exposure to ticks is recognized, ECM followed by other neurologic, cardiac, or joint involvement suggests the diagnosis. Other cases that occur within the endemic areas may be suspected because of typical organ involvement, despite the absence of ECM and the lack of recognized exposure to ticks. Of all the patients with Lyme disease in Connecticut, 83% of the patients studied had erythema migrans; 24% had arthritis; 8% had neurologic manifestations; and 2% had cardiac involvement. For those with arthritis, affected joints were the knee (89%), hip (9%), shoulder (9%), ankle (7%), and elbow (2%). Persons under 20 years of age were 1.6 times more likely to have arthritis than persons over 20 (7/100000 compared with 4/100000), while both groups were equally likely to develop ECM (13/100000). Seventy-nine percent of patients with arthritis did not report antecedent erythema migrans.

The clinical manifestations of Lyme disease occur in stages that roughly parallel their chronologic appearance. Stage 1 is characterized by ECM and non-specific influenza-like

symptoms that occur 3 to 32 days after exposure to ticks. ECM itself begins as an erythematous papule or macule, which gradually becomes an annular lesion that can be many centimeters wide. Some lesions are less distinctive. Secondary lesions may occur at a distance from the original tick bite. Stage 2 often occurs weeks to months after stage 1. Neurologic or cardiac abnormalities develop in 15% and 8% of cases, respectively. Patients may have signs of meningitis, encephalitis, cranial neuritis, motor or sensory radiculoneuritis, and possibly myelitis. Either tachycardia or bradycardia may occur, in association with variable degrees of atrioventricular nodal block. Rarely is there evidence of pericarditis or myocarditis. Stage 3, typified by arthritis, occurs in about 60% of cases. Synovitis may first be manifested weeks to years after ECM. Characteristically, the synovitis affects the knees, but other large joints may be involved as well.

At each stage, symptoms and signs frequently wax and wane. Some symptoms are self-limited regardless of therapy. No deaths from Lyme disease have been reported.

LYME DISEASE IN PREGNANCY

Transplacental transmission of the vector, *Borrelia burgdorferi*, has been documented: the patient, a pregnant woman with Lyme disease who did not receive antimicrobial therapy, delivered an infant with a congenital heart defect. More cases are likely to be reported which will delineate the organism's potential for an adverse impact on the developing fetus.

DIAGNOSIS

The diagnosis of early Lyme disease remains primarily clinical. The CDC's case definition is presented in Table 50.1.

The erythrocyte sedimentation rate is often mildly elevated. Likewise, the serum concentration of IgM may be elevated, and IgM- or IgG-containing cryoglobulins may be detected. The patient may have lymphopenia. Serum transaminase activity may be increased if mild hepatic involvement is present. During the later stages of Lyme disease, characteristic changes occur in the cerebrospinal fluid. None of these abnormalities, however, is diagnostic.

Serologic studies have been developed for measuring the antibody response to the infecting spirochete. These tests include the indirect immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA). The IFA for the Lyme disease spirochete is analogous to the fluorescent treponemal antibody assay for detection of antibodies to *Treponema pallidum*. *Borrelia burgdorferi* spirochetes from a known source are fixed to a microscope slide. The patient's serum is incubated on the slide. The slide is washed, over-layered with fluorescent antihuman immunoglobulin, and washed again. Then it is examined by fluorescence microscopy. If the patient's serum contains antibody to the spirochete, the latter will fluoresce. The ELISA for

Table 50.1 Centers for Disease Control case definition for Lyme disease

Clinical description

A systemic, tick-borne disease with protean manifestations, including dermatologic, rheumatologic, neurologic, and cardiac abnormalities. The best clinical marker for the disease is the initial skin lesion, erythema migrans, that occurs among 60–80% of patients

Clinical case definition

- Erythema migrans (>5 cm in diameter), or
- At least one late manifestation (i.e. musculoskeletal, nervous, or cardiovascular system involvement) and laboratory confirmation of infection

Laboratory criteria for diagnosis

- Isolation of *Borrelia burgdorferi* from clinical specimen, or
- Demonstration of diagnostic levels of IgM and IgG antibodies to the spirochetes in serum or cerebrospinal fluid, or
- Significant change in IgM or IgG antibody response to *B. burgdorferi* in paired acute- and convalescent-phase serum samples

Case classification

Confirmed: a case that meets one of the clinical case definitions above

(from *MMWR* 1991; 40:417)

Lyme disease uses an extract of the *Borrelia burgdorferi* spirochete. The extract is bound in an assay-well to which the patient's serum is added. After a brief incubation, the well is washed, and alkaline phosphatase conjugated with antihuman immunoglobulin is added. It is washed again to remove unbound immunoglobulin, and any antibody from the patient's serum that specifically binds is detected by a colorimetric assay for alkaline phosphatase activity.

Physicians should be aware of the limitations of current tests. Sensitivities of the IFA and the ELISA are relatively low during stage 1, and the antibody response can be curtailed or aborted by early treatment with antibiotics. In contrast, some research laboratories have reported sensitivities >95% for tests of patients with stage 2 or 3 Lyme disease. Test specificities approaching 100% have also been reported; however, considerable variability may occur among laboratories because the tests are not standardized and are difficult to perform. The sensitivities and lack of standardization of the tests preclude their use alone for routine disease reporting and reinforce the need to develop a reliable and practical case definition for surveillance that is not dependent on serologic test results. False-positive results have been reported in Lyme disease assays. Serum samples from patients with treponemal diseases, including syphilis, yaws, and pinta, have considerable cross-reactivity in the tests for antibody to *Borrelia burgdorferi*. In a study by the CDC, one patient each with systemic lupus erythematosus and rheumatoid arthritis had elevated titers. Patients with infectious mononucleosis, relapsing fever, and leptospirosis have been described by others to be reactive to some degree.

THERAPY

Because antimicrobial therapy decreases the morbidity from Lyme disease, it is important that cases be recognized and patients treated. In endemic areas, Lyme disease can be diagnosed if the typical ECM skin lesion is present. Serologic tests have been developed to measure antibody against *Borrelia burgdorferi*. These tests, when positive, can help support the clinical suspicion of Lyme disease in atypical cases, such as those without ECM or those occurring outside recognized endemic areas. However, serologic tests are often negative, particularly early in Lyme disease. Therefore, a negative result does not exclude the diagnosis early in the course of the illness. Antimicrobial therapy with an oral tetracycline is recommended for patients with early manifestations of Lyme disease. Children and pregnant women should be treated with large doses of penicillin or erythromycin. Some of the neurologic abnormalities, as well as established arthritis, have been found to respond to high-dose intravenous penicillin.

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51
Leptospira

Leptospira organisms are slender, round, active, mobile spirochetes with one or both ends bent in the form of a hook. They are generally between 5 and 15 μm long and, unlike *Treponema pallidum*, they are readily cultured on relatively simple bacteriologic media. Virtually all of the pathogenic leptospires are represented in the *L. interrogans* group. Although there are over 100 serotypes of *L. interrogans*, the great majority of infections in man are from the following serotypes: *L. icterohaemorrhagiae, L. canicola, L. grippotyphosa, L. pomona, L. hebdomidis, L. mitis, L. bovis, L. autumnalis*, and *L. kasman*.

Leptospirosis is an infection of worldwide distribution. In the United States disease is observed within certain occupations which involve contact with animals or as a consequence of recreational activities such as hiking, swimming, canoeing, etc.

Leptospiral infection is common among many wild and domestic animals including rodents, livestock, wild mammals, dogs, and cats. Human infection occurs either through direct contact with an infected animal or indirectly through contact with water or soil contaminated by the urine of infected animals (Figure 51.1). The spirochetes can survive in untreated water for months. Person-to-person contact is at best rare.

Leptospirosis is endemic in the tropics. *Leptospira* proliferate in fresh water, damp soil, vegetation, and mud. The occurrence of flooding after heavy rainfall facilitates the spread of the organism because, as water saturates the environment, *Leptospira* present in the soil pass directly into surface waters.

The incubation period is said to vary from 7 to 12 days (range, 2–20 days). This variation in the incubation period is in part a function of the inoculum size and host defense mechanisms. Subsequent leptospiral replication results in a prolonged leptospiremia with widespread dissemination of the spirochetes through the body. There is a tendency for preferential localization within kidneys, adrenals, liver, meninges, and lungs.

In the United States, clinically recognized illness exhibits a seasonal pattern in which the majority of cases occur in the months of July through October. The ensuing pattern of infection can be subdivided into two distinct phases, the first characterized by leptospiremia and the second by leptospiruria which is associated with the development of immunity.

Only a minority of patients for whom occupational data were available had apparent job-related illness. Most individuals acquire their infection while engaged in non-vocational activities. The most probable sources of infection were surface water (ponds, creeks, or sewage systems) which accounted for 29%, dogs (22%), rodents (11%), and cattle or swine (8%).

The phase of leptospiremia is characterized by clinical manifestations of an acute systemic infection which persists for 7–8 days.

Two distinct clinical presentations occur. The vast majority of patients present with a mild anicteric febrile illness. Approximately 10% develop full-blown Weil’s syndrome with jaundice, fever, rigors, severe myalgias, severe conjunctivitis, diarrhea and skin

rashes. Manifestations of more severe disease may include renal failure, pulmonary hemorrhage, and hemodynamic collapse. The spirochetes are demonstrable within the blood and cerebrospinal fluid (CSF). This phase of the disease leads either to death or to defervescence and symptomatic improvement.

When the latter occurs, the leptospires are no longer demonstrable in either blood or CSF. Because of the multiplicity of potentially involved organ systems, a wide spectrum of clinical signs and symptoms may be elicited. Characteristic is the marked prostration which tends to override other clinical signs. Engorgement of the small conjunctival vessels is very common. Jaundice

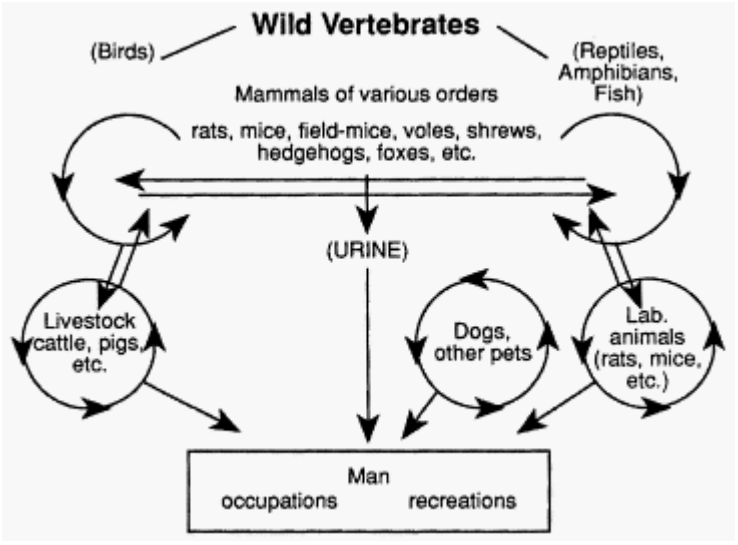

Figure 51.1 Relationships of the principal reservoir hosts of *Leptospira* (Turner LH. *Trans R Soc Trop Med Hyg* 1967; 61:842)

may occur while the patient is febrile and in a period of clinical deterioration. The anticipated case fatality is of the order of 2–4%.

With the appearance of specific antibodies, leptospiral organisms are removed from blood and tissues by phagocytosis. The one exception to this appears to be the kidney, where organismal replication within the renal medulla persists, resulting in prolonged shedding of the organisms, first into the urine and then into the extracorporeal environment. This carrier-shedder convalescent phase persists for one or two months.

Fever and earlier symptoms may reoccur in some patients. These patients are prone to exhibit signs of central nervous system involvement, such as headaches, photophobia, and nuchal rigidity. Complications such as optic neuritis, uveitis, iridocyclitis, chorioretinitis and peripheral neuropathy may occur during the phase of leptospiruria.

INVOLVEMENT OF THE PRODUCTS OF CONCEPTION

It is not uncommon for a gravida to abort during leptospiremia. The high rate of abortion and miscarriages in certain rice-growing areas of China where leptospirosis is an occupational hazard is frequently cited in the literature. Chang has demonstrated that intrauterine infection of the human fetus can occur. He isolated leptospires from the liver and kidney of a 5-month abortus of a patient suffering from leptospirosis due to serotype *kasman*.

Lindsay and Luke reported a fatal case of leptospirosis occurring within hours of parturition, presumably due to intrauterine infection. Histologic analysis revealed extensive hepatocellular necrosis with relative sparing of the periportal areas. Sections of the kidneys demonstrated extensive tubular epithelial cell degeneration involving particularly the proximal and distal convoluted tubules. Leptospires were demonstrated in both organs. Of note was the fact that the maternal illness was subclinical. Apparently, attenuation of maternal infection did not impair the ability of the organism to traverse the placental barrier.

The diagnosis of congenital disease necessitates the presence of illness at birth or within the first 48 hours. Although congenital infection occurs, it is probable that the bulk of fetal wastage observed is secondary to maternal disease and not fetal involvement *per se*.

DIAGNOSIS

Definitive diagnosis of leptospirosis is contingient upon laboratory identification of the spirochete. The laboratory criteria for leptospirosis are (1) isolation of leptospira from a clinical specimen, (2) fourfold or greater increase in serological titer between acute and convalescent serum obtained at least 2 weeks apart and run in the same test, and (3) demonstration of leptospira in tissue specimens by immunohistochemistry or immunofluorescence.

During leptospiremia, the organisms may be demonstrated by darkfield microscopic analysis of blood samples (including the clot) and the CSF. Thin and thick blood smears should be obtained before meals to avoid lipemic samples.

Isolation can be achieved using weanling mice or special semisolid, protein-supplemented media, such as Fletcher, Stuart, or polysorbate 80-albumin media. Blood, CSF and tissues provide the highest yields in the first 2 weeks of illness. Thereafter urine becomes the testing specimen of choice.

Even in the hands of the experienced worker, dark-field microscopy results in failure or misdiagnosis so frequently that it should never be used as the sole diagnostic test.

The microscopic antileptospiral agglutination test is the most commonly used immunologic method use for the detection of specific antibodies. Testing requires acute and convalescent sera obtained at least 2 weeks apart. Other test include enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody test, and indirect hemagglutination test, among others.

Fluorescein-labeled antileptospiral globulins afford a means of establishing a definitive diagnosis for organisms identified in tissue, blood, urine, or bacteriologic

cultures. The only limiting factor is the relatively narrow range of serotypes encompassed.

A potential, but rarely used, ancillary procedure is biopsy of the patient's gastrocnemius muscle during the acute phase of illness. The spirochetes can occasionally be demonstrated by use of the Levaditi staining method. Muscle necrosis and a mononuclear cell infiltration associated with perivascular cuffing may aid in suggesting the diagnosis.

Table 51.1 Advocated antibiotic regimens in the treatment of infection with *Leptospira*

Drug of choice	***Dosage***	***Duration of therapy (days)***
Penicillin	2.4 to 3.6 million units in divided doses	7
Doxycycline*	100 mg did	7

*The use of doxycycline is contraindicated in pregnancy

THERAPY

Penicillin is the antibiotic of choice (Table 51.1). The dosage depends on the duration of the illness, its severity, and the general condition of the patient.

In the non-pregnant patient, doxycycline 100 mg twice a day for 7 days constitutes an alternate effective therapy.

As with any of the treponemal diseases, antibiotic therapy may result in the production of a Jarisch-Herxheimer reaction resulting in a sharp rise in temperature, hypotension, and precipitation and aggravation of the prevalent signs and symptoms. When possible administration of the initial antibiotic dose should be given by the intravenous route with either a central line catheter or multiple intravenous lines in place. The ability to increase blood oxygenation, combat hypotension, and counter hyperthermia should be available.

The earlier the treatment is started, the more likely it is that complications and existing symptoms will be modified. Specific impairment of hepatic and renal function requires individualization of therapy. Analgesics and hot compresses are effective in relieving the myalgia and arthralgia so common during leptospiremia.

Supportive therapy is indicated for treating dehydration, hypotension, hemorrhage, and renal failure.

Oral doxycycline (200 mg weekly) may provide effective chemoprophylaxis for persons with short-term exposure in environments associated with increased risk for infection. Persons participating in recreational water activities in areas where leptospirosis is endemic may be at increased risk for the disease, particularly during periods of flooding, and should consider preventive measures such as wearing protective clothing and minimlizing contact with potentially contaminated water.

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52
Treponema pallidum (syphilis)

Treponema pallidum is an elongated spiral organism, the morphology of which differs markedly from that of other bacteria. The spirochete is 5–20 μm long and approximately 0.2 μm thick. Electron microscopy reveals an outer enveloping membrane, the periplast, contoured to give between 4 and 14 spirals. Within the underlying protoplasmic cylinder is an axial filament composed of several fibrils. The outer envelope is between 70 μm and 90 μm thick, lying between two membrane bundles of fibrils that are stretched from one end of the treponeme to the other and wind in helical coils. The marked thinness of the organism renders it relatively non-detectable by light microscopy. The presence of muramic acid suggests the existence of a cell wall component which is thought to be the reason for the therapeutic effectiveness of penicillin. *Treponema pallidum* grows best at 34 to 35ºC both *in vitro* and *in vivo*. The sensitivity of the organism to elevated temperature (*T. pallidum* is destroyed at 105ºF [40.5ºC]) had long been clinically noted and constituted the basis for the efficacy of artificial fever therapy in the treatment of tertiary syphilis.

IMMUNOLOGY OF INFECTION

The initial response to infection with *T. pallidum* results in the synthesis of predominantly IgM antibodies early in the disease. Within two weeks antibodies of the IgG type are produced. They appear to be the prime mediator of immunity. With early eradication of disease, there is loss of immunity to infection. In contrast, the development of latency is associated with relative immunity to reinfection.

What causes the ultimate destruction of *T. pallidum is* controversial. It is currently postulated that the destruction of the organisms occurs extracellularly. The histologic lesions caused by *T. pallidum* suggest that both humoral immunity (immobilizing antibodies, plasma cells) and cellular immunity (lymphocytes) play an important role in its eradication.

The seroresponse of women treated for primary or secondary syphilis is such that the VDRL should decline approximately fourfold at three months and eightfold at six months. Failure of the VDRL to change significantly with time should alert the physician to possible treatment failures or reinfection.

NATURAL HISTORY OF THE DISEASE

Syphilis is an infection of mucous membranes. Transmission of the spirochete is predominantly the result of coitus. In the female the primary lesion may occur on the labia, vaginal wall, or cervix. Extragenital sites, depending on sexual proclivities, are not uncommon.

Adequate sexual exposure is not the sole determinant of infection. Infection develops in only 10% of human volunteers from a single sexual encounter. In clinical situations, almost two-thirds of individuals intensively exposed to syphilis in its infectious stage will acquire infection. It is probable that *T. pallidum* can breach the mucous membrane barrier, but it is equally probable that minute breaks in the membrane in many instances provide the true portal of infection. Treatment during incubation is almost 100% effective and should be considered mandatory in the management of persons exposed to infectious syphilis. The time required for development of the primary lesion is partly a function of the number of organisms establishing the initial infection and their subsequent replication at the portal of entry. Infections with a large inoculum (e.g. 10^7 organisms) may cause a chancre in 5 to 7 days.

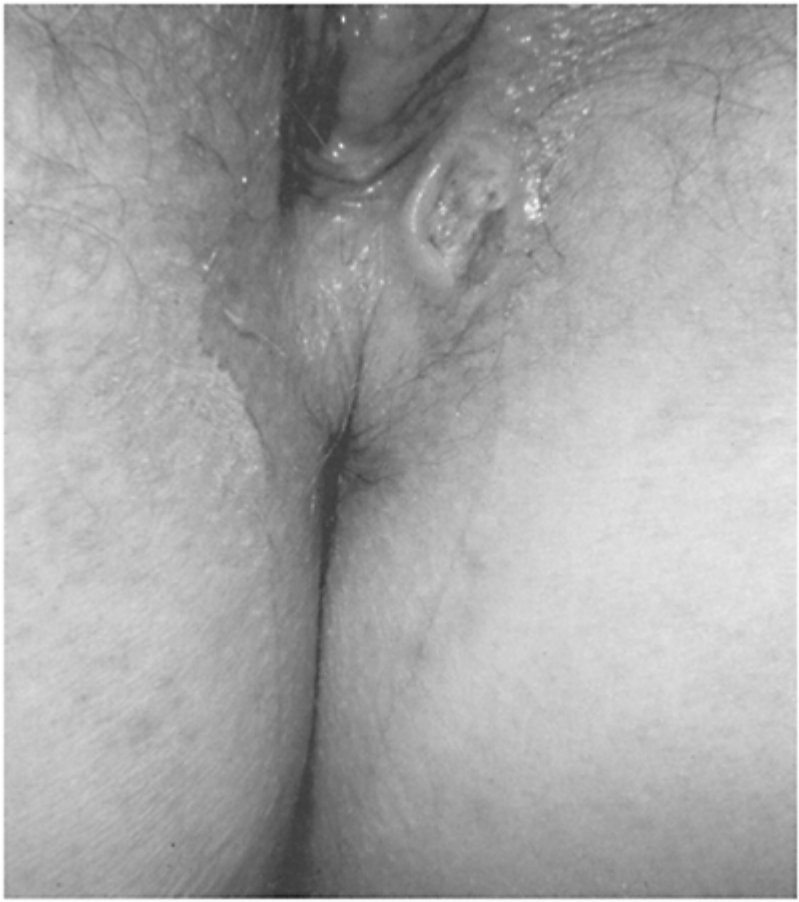

Figure 52.1 Classical chancre

The inoculation of 50 to 100 organisms is followed by an incubation period of about three weeks. The longest incubation period appears to be approximately five weeks. The

prolonged incubations reflect the fact that the division time of *T. pallidum* is about 33 hours, compared to minutes for other bacteria.

Primary syphilis

Once *T. pallidum* has penetrated the epithelial layer, the organisms replicate locally. During this period, proliferation of treponemes is associated with stimulation of cell-mediated and humoral immunity Sensitized thymus-dependent lymphocytes appear in primary syphilitic lesions. Ingestion of the treponemes initially by polymorphic neutrophils and later by macrophages leads to antigen processing. In the presence of specific antibodies, the number of viable organisms declines. The presence of a variety of antibodies can be demonstrated in the serum of most (80% or more) but not all patients seeking medical attention for syphilis.

By the time the primary lesion is detected, both humoral and cell-mediated immune mechanisms have been activated. Classical chancres are solitary lesions (Figure 52.1). However, multiple chancres have been identified in up to 40% of individuals with primary syphilis. Genital chancres are frequently atypical. A high index of suspicion is required for their diagnosis.

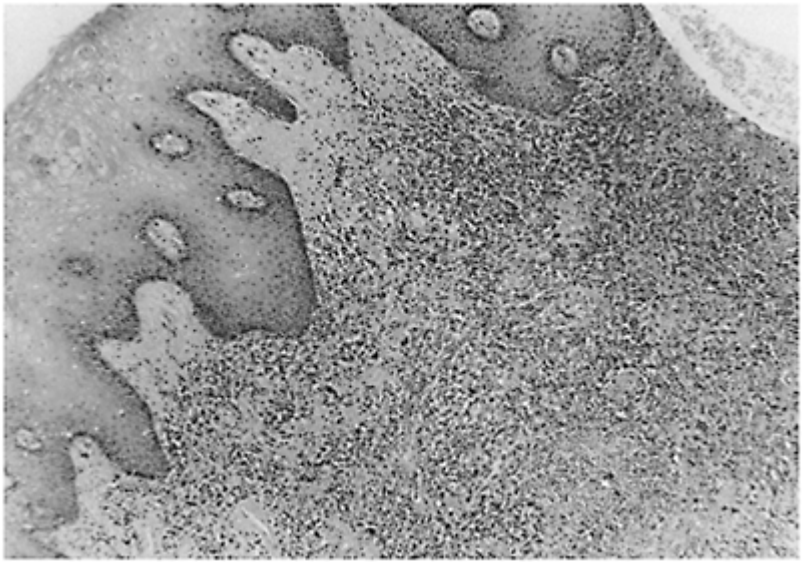

Figure 52.2 Histologic section of biopsy, revealing extensive lymphocytic and plasma cell infiltration of the underlying connective tissue. Marked endothelial proliferation is present (H&E, ×260)

Regional adenopathy normally accompanies the chancre of primary syphilis. The adenopathy usually develops a week after the appearance of the initial lesions. Untreated, a chancre will persist for two to eight weeks and then spontaneously disappear.

Macroscopically, the primary lesion consists of a small papule which breaks down to form a superficial, painless ulcer with a clean granular base and firm scrolled margins. Histologic analysis reveals, in the absence of secondary infection, an extensive plasma cell and lymphocytic infiltration (Figure 52.2). Characteristic of the lesion is the effect of treponema on the small blood vessels. Extensive endothelial proliferation in association with a significant plasma cell infiltrate should suggest a diagnosis of primary syphilis on histologic grounds alone.

The organism is not detectable by conventional staining techniques that utilize the ability of silver salts to delineate the organisms' contours or by darkfield microscopy of a wet preparation from the primary lesion.

Most frequently, dissemination from the portal of infection to the regional lymph nodes occurs during the primary phase of the disease, with the result being 'satellite' buboes. Physical examination reveals enlarged, firm but tender lymph nodes, reflecting both organismal replication and reticular and lymphocytic cellular proliferation.

Irrespective of the subsequent clinical course, the chancre heals spontaneously. In approximately 30% of the cases disease is limited to replication at the portal of entry, and even without therapy, eradication of the infection may occur in conjunction with the disappearance of serologic evidence of syphilitic infection as measured by non-treponemal tests.

From regional lymph node drainage of the portal of infection, hematogenous dissemination characteristic of the secondary phase of the disease occurs.

Secondary syphilis

The interim between the primary and secondary phases is in part a function of the time required for the development of the primary lesion and its satellite buboes. The secondary stage of syphilis usually manifests 3 to 6 weeks after the primary chancre has occurred. The lesions of secondary syphilis are the consequence of:

(1) hematogenous dissemination; and
(2) selective replication of treponemes at sites of slightly reduced body temperature which afford more optimal conditions for replication, i.e. skin and mucous membranes.

The secondary phase is characterized by a generalized eruption, primarily on mucous membranes, the palms of the hands, and the soles of the feet. Cutaneous involvement is merely a reflection of widespread organ colonization. Clinically recognizable lesions have been observed in almost every organ system. Nevertheless, signs and symptoms referable to this extensive involvement are uncommon. An individual, during the secondary phase of syphilis, may exhibit bone tenderness when pressure is applied. In rare instances, iritis and alopecia occur.

The cutaneous lesion of the secondary stage of syphilis is a papular lesion, except in intertriginous areas where it is condylomatous. In the latter areas the papules are circumscribed, flat, and moist and tend to become confluent (Figure 52.3 A and B). The

lesions contain large numbers of spirochetes. The patient is again capable of transmitting disease and must be regarded as highly infectious to those in the immediate environment. A mucous membrane in which lesions are present is a potential locus for infection and dissemination. This predilection for cutaneous and mucous membranes appears to reflect *T. pallidum's* ability to replicate more rapidly at a temperature slightly below that of the internal body. It is in the late phase of primary illness and the second stage of the disease, during which hematogenous dissemination is occurring, that *T. pallidum is* afforded the opportunity to traverse the placenta and infect the conceptus. The depression of cellular immune responses to *T. pallidum* may in some way be involved in recrudescence of active lesions in secondary syphilis. The character of the lesions is partially governed by the induced systemic immunity. Rather than appearing like primary chancres, the appearance is that of a localized inflammatory lesion. If systemic immunity fails to develop, a florid type of infection called malignant secondary syphilis occurs in which the secondary lesions resemble the primary chancre. The small multiple lesions of the disseminated stage of acquired syphilis persist from weeks to months. Patients with this stage of disease have high antibody titers to both specific treponemal and non-treponemal antigens. Circulating antigen-antibody complexes can be detected at this stage of infection and may lead to immune complex deposition in the kidneys. While the host is unable to contain the initial infection, intradermal rechallenge with *T. pallidum* is unlikely to induce a chancre. This situation, in which the host resists rechallenge but is unable to clear the initial infection, is called premunition.

Latency

The third stage, latency, is a stage of disease in which systemic immunity of the host is sufficient to suppress all morphological evidence of treponemal replication. Whether subsequent disease (tertiary syphilis) develops is a partial function not only of combined cell-mediated immunity and humoral immunity but also of organismal virulence. Virulent treponemes display a remarkable capacity to resist attempts of both humoral and cellular host responses to eradicate them. Termination of active systemic infection probably requires the interaction of both types of immunity. Secondary relapses during latency occur in 25% of untreated patients, primarily in the first year of latency. In the remaining cases, relapse occurs in the ensuing five years. This first year

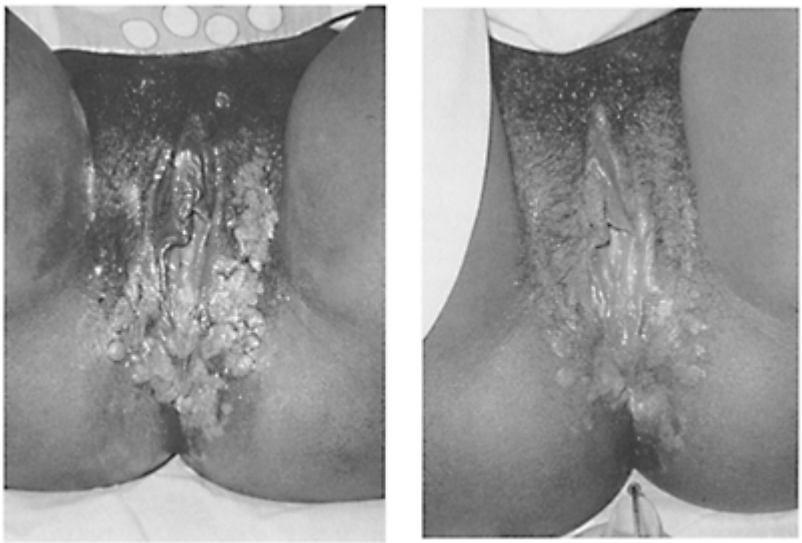

Figure 52.3 Secondary syphilis (A) Manifestations of secondary syphilis (extensive condylomata lata) in intertriginous areas. (B) Same patient after five days of penicillin therapy

period is called early latency. Tertiary syphilis appears one to 20 years after the induction of latency. The sites of lesions are no longer influenced by temperature considerations. Gumma appear in soft tissue and viscera. The relative absence of or the difficulty of demonstrating intact treponemes has suggested that these lesions are the partial consequences of the immune state. While visceral involvement tends to be the rule, gumma may appear subcutaneously. They have a predilection for areas of trauma such as the elbows and knees. The most common problem encountered is how to handle the asymptomatic patient with untreated syphilis of more than one year's duration. Wiesel compared treatment with 7.2 million units of penicillin G benzathine with and without performing a lumbar puncture. Based on subsequent cerebrospinal fluid analysis, both strategies resulted in a cure rate of at least 99.7%. Lumbar puncture offers little or no additional benefits and is not cost effective in patients with asymptomatic late syphilis provided that therapy is that for neurosyphilis.

DIAGNOSIS

Confirmation of a syphilitic chancre depends on the demonstration of *T. pallidum* on dark-field microscopic examination. The lesion should be cleansed and abraded with gauze to induce superficial bleeding, and the blood blotted away. Once the serum begins to ooze, a small aliquot is then placed on a glass slide and a cover slide applied. Darkfield

analysis should be completed before the slide dries. If a specimen must be transported a short distance, the serum specimen should be collected in a relatively large-bore capillary tube and one end temporarily sealed with clay.

The serologic tests for the detection of *T. pallidum* can be broken down into two broad categories: nontreponemal (flocculation and complement-fixation tests) and treponemal (*T. pallidum* immobilization [TPI], *T. pallidum* microhemagglutination [TPHA], fluorescent treponemal antibody [FTA] tests), serum enzyme-linked immunosorbent assay (ELISA) test, polymerase chain reaction (PCR), and serum IgM Western blot assay. The former are serologic assays for antibodies that react with cardiolipin, a non-specific antigen; the latter, by using *T. pallidum* or an avirulent strain of *T. pallidum*—known as the Reiter treponeme—as the test antigen, detect specific antibodies.

The flocculation tests for syphilis utilize a cardiolipinlecithin complex chemically extracted from beef heart. Cardiolipin constitutes about 15% of treponemal lipids and is present in mammary tissues. It is not clear whether the antibodies detected are directed against altered mammilar tissue or against treponeme-incorporated mammilial lipids.

The flocculation tests represent the combination of cardiolipin antigen with antibodies directed against comparable antigenic determinants (reagin); the combination precipitates grossly so as to form a visible aggregate. These tests tend to be highly sensitive for the late primary and the secondary stages of infection and are utilized for rapid screening. Flocculation tests may be performed on a slide [VDRL slide, Kline, Mazzini), in a tube (VDRL tube, Hinton), or on specially treated cards.

Since both the flocculation and complement fixation tests are non-treponemal, clinical cases are found in which positive test results may be detected in the absence of syphilitic infection. These biologic positive tests are due to substances in the patient's serum that react like the reagin antibody and result in positive flocculation or complement fixation reactions. Biologic false-positive reactions have been identified in patients with evidence of drug abuse, malaria, leprosy, vaccinia, infectious mononucleosis, and certain other viral infections. However, any febrile disease or immunization procedure may be associated with a false-positive serologic test. Biologic false-positive reactions of long duration have been identified in collagen disorders (such as rheumatoid arthritis and systemic lupus erythematosus [SLE]), sarcoid, and lymphomas.

The significance of a positive non-treponemal test should be confirmed by a treponemal test.

False positive VDRL test

The identification of a positive VDRL test necessitates:

(1) determining whether it is causally related to infection with *T. pallidum;* and
(2) evaluating the stage of the disease process.

Biologic false-positives occur in roughly 1% of patients. These VDRL tests are usually of low titer and not associated with a positive FTA test except in patients with SLE. Approximately 10% of SLE patients exhibit an atypical fluorescent pattern in which the usual homogeneous pattern of fluorescence is replaced by the organism assuming a beaded appearance. Unless the characteristic pattern of fluorescence can be identified, an

alternative explanation for a positive test must be sought. A positive VDRL test in conjunction with a negative FTA-ABS test is not indicative of infection with *T. pallidum*.

THERAPY

Once a causal relationship is inferred, clinical staging of the disease process in terms of primary, secondary, latent tertiary, or neurosyphilitic stages should be attempted, since the clinical staging has therapeutic implications; that is, the patient is treated according to the stage of the disease (Table 52.1). In primary or secondary syphilis, fetal as well as maternal indications for therapy are applicable. Analysis of the cerebrospinal fluid (CSF) to identify those patients with already established neurosyphilis is imperative since the dosage and duration of therapy are different for neurosyphilis than for other stages. A gravida with a positive low-titered VDRL and a positive FTA-ABS test, in the absence of clinical evidence of infection, should be treated as if she had late latent syphilis (Table 52.2). If a diagnostic lumbar

Table 52.1 Advocated antibiotic regimen for the treatment of syphilis in pregnancy

Drug of choice	***Dosage***	***Duration of therapy (days)***
Primary or secondary (infectious) syphilis in first and second trimester		
Benzathine penicillin G*	2.4 million units total (1.2 million units in each buttock) at a single session; route of administration: IM	–
or		
Aqueous procaine penicillin G	4.8 million units total: 600000 units daily; route of administration: IM	8
Primary or secondary (infectious) syphilis in third trimester		
Benzathine penicillin G	2.4 million units followed by 1.2 million units at each of the next 3 clinic visits, 4 days apart; route of administration: IM	–
Latent syphilis of less than one year's duration		
Benzathine penicillin G*	2.4 million units total at a single session; route of administration: IM	–
Latent syphilis of indeterminant or more than one year's duration†		

Benzathine penicillin G	7.2 million units total: 2.4 million units weekly for 3 successive weeks; route of administration: IM	–

*Benzathine penicillin G is the drug of choice because it provides effective treatment in a single visit.
†Cerebrospinal fluid examination is recommended in any patient with syphilis of greater than 1 year's duration to exclude asymptomatic neurosyphilis

puncture is not performed, the patient needs to be treated as an asymptomatic neurosyphilitic. The key to successful therapy is as much the time interval during which antibiotics are administered as it is the actual dosage.

Clinical staging of the disease becomes more important when the physician is confronted with a patient who has a documented reaction to penicillin. The alternate drugs of choice, namely, erythromycin and tetracycline, have limited application in the gravida. Erythromycin traverses the placental barrier, but inefficiently. Fetal plasma levels are about 6–20% of maternal plasma levels. Adequate maternal therapy may not abort infection in the fetus. As was previously stated, tetracycline is contraindicated in the gravida. The experimental evidence that tetracycline is a teratogen if it is given during the period of osseous organogenesis is almost as incriminating as that which existed for thalidomide. Its therapeutic use in the second and third trimesters, the periods of growth and differentiation, results in retardation and hypoplasia of the deciduous teeth and inhibition of bone growth.

Given a gravida in the first trimester with either primary or secondary syphilis, early latent syphilis or a high VDRL and documented penicillin hypersensitivity, it is advocated that she be brought into a controlled environment (preferably hospitalized) and treated by desensitization and penicillin therapy. Infection in the second or third trimester should be treated with erythromycin, and the infant should be retreated in the neonatal period with penicillin. Even inadequate therapy, while not aborting infection, does retard its progression.

The reversion to seronegativity of the nontreponemal type of test is a function of the stage of the disease as well as of the efficacy of therapy. A serologic cure will be achieved sooner in the early stage of syphilis, whereas for patients in the late stages, a serologic cure may never be realized.

Table 52.2 Therapy for latent or indeterminant syphilis of more than one year's duration in pregnancy

Benzathine penicillin G	7.2 million units total: 2.4 million units weekly for three successive weeks; route of administration: IM

In a patient who has primary syphilis and a darkfield-positive ulcer, a positive nontreponemal test may not develop until after the initiation of therapy. The test reverts,

usually within three months, unless reinfection or relapse occurs. Six to nine months may pass before the patient's serum becomes negative. Any patient whose serum fails to become negative nine months after treatment should be retreated.

THERAPEUTIC FAILURE

Up to a 2% incidence of therapeutic failures can be anticipated with one course of adequately administered penicillin in the treatment of primary syphilis. Patients in the secondary stage of syphilis invariably have positive reagin tests. Immediately after treatment, the serologic titer usually rises and then pursues a downward pattern. Within one year about 98% of patients will become seronegative. The remaining 2% should become seronegative during the second year. As with primary syphilis, if the expected serologic response is not observed, the patient should receive a lumbar puncture and then be retreated within one year after the initial treatment. The CSF should be examined for cell count and protein; a VDRL test should also be performed. If any of the CSF tests are abnormal, the patient should be treated for neurosyphilis.

PENICILLIN DESENSITIZATION DURING PREGNANCY

The presence of allergy against the minor determinants of penicillin in a gravida with syphilis presents a major therapeutic problem. This clinical situation has been successfully addressed by oral or intravenous penicillin desensitization. Ziaya *et al.* described a woman with an allergy against both major and minor determinants of penicillin in whom syphilis was diagnosed on routine

Table 52.3 Regimen of Van Arsde for incremental intravenous penicillin G infusion

Concentration (U/ml)	*Volume (ml)*	*Duration (min)*
001	50	30
1.0	50	30
10	50	30
100	50	30
1000	50	30
10000	50	30
100000	50	30

(Ziaya PR *et al. J Am Med Assoc* 1986; 256:2561)

obstetric screening. The patient underwent desensitization utilizing graduated intravenous doses of penicillin followed by treatment with a constant infusion for eight days. She experienced no serious allergic reactions requiring alteration of therapy. Wendel *et al.*

reported on 15 pregnant women with histories of penicillin allergy confirmed by positive immediate wheal-and-flare skin tests. Thirteen women had syphilis, one *Listeria* sepsis and one *Streptococcus viridan's* endocarditis. Each patient was desensitized over four to six hours by oral administration of increasing doses of penicillin V. At the completion of the procedure, bolus dose parenteral therapy with penicillin G or ampicillin was instituted. Five of the subjects (33%) experienced either pruritis (three) or urticaria (two). No interruption of desensitization or therapy was necessary. All clinically apparent maternal infections were cured. The pregnancy complicated by listeriosis aborted in the first trimester. No cases of congenital syphilis were identified. These studies indicate that oral or intravenous desensitization is an acceptable, safe approach to therapy of syphilis in gravida with documented hypersensitivity to penicillin and should be initiated in an intensive care unit with staff for intubation and management of anaphylaxis. The method of Van Arsde was utilized by Ziaya *et al.* In this regimen, aliquots of 50 ml were infused, each containing a tenfold increase in the concentration of penicillin G beginning at 0.01 U/ml and reaching 100000 U/ml (Table 52.3). Each aliquot was administered over a period of 30 minutes. Once desensitization was achieved, a continuous infusion of aqueous penicillin G at 25000 U/h was given to maintain a blood level to cover at least three replications (more than 30 hours per replication) of *T. pallidum*.

IMPACT OF HIV INFECTION ON SYPHILIS

Patients with AIDS represent only a minority of the total number of T-cell-deficient patients with HIV disease. The T-cell deficiency has caused severe complications when live-virus vaccines are inadvertently administered to recipients with impaired immunologic function due to HIV.

Several investigators have reported the subsequent development of neurologic complications following standard penicillin therapy in patients infected with HIV. These reports have suggested that penicillin alone is probably not adequate to eradicate infection in the absence of a vigorous host response. The immunologic response of the patient appears to be important in controlling the infection, even in the presence of adequate antibiotic therapy. What is implied is that everyone with HIV infection who contracts syphilis must be treated with higher doses of antibiotics for prolonged periods. The antibiotic therapy for neurosyphilis appears to be the minimal acceptable regimen (2.4 million units aqueous penicillin IV for 8–10 days.)

JARISCH-HERXHEIMER REACTION

The issue of therapy is further complicated by the potential adverse host response to penicillin at the placental level. Klein *et al.*, monitored thirty-three gravidas with syphilis for 24 hours after treatment with benzathine penicillin G. Fifteen (40%) of the women had a Jarisch-Herxheimer reaction. Twelve of the fifteen patients had secondary syphilis. The incidence of a Jarisch-Herxheimer reaction among the 20 gravidas with secondary syphilis monitored was 60%. The most common symptoms were fever (73%), uterine contractions (67%), and decreased fetal movement (67%). The signs or symptoms began

2–8 hours after treatment; fevers peaked at 6–12 hours post-therapy and the events usually abated by 16–24 hours after treatment. Uterine contractions and decreased fetal activity began concurrent with maternal fever in eight of ten women reporting contractions. Transient late decelerations were detected in three of 11 monitored patients. Three of the women with Jarisch-Herxheimer reactions delivered infants with congenital syphilis, including one stillbirth, but none of those without a detectable reaction had fetal treatment failures. The Herxheimer reaction that is sometimes induced by therapy may not be limited to the maternal host.

Approximately 10–25% of pregnant women with secondary syphilis in whom a Jarisch-Herxheimer reaction develops will experience an intrauterine demise within one to four weeks. Why these fetuses subjected to a Jarisch-Herxheimer reaction die is a matter of conjecture. Induction of acute placental insufficiency by additional compromise of the placental vasculature is a distinct possibility. The sustained hyperthermia associated with Jarisch-Herxheimer reaction may be either a significant co-factor or the principal catalyst in these late gestational fetal deaths.

About 9% of patients with secondary and early latent syphilis will exhibit a Jarisch-Herxheimer reaction several hours after the first injection of penicillin. The reaction is characterized by chills, fever, headaches, myalgia, and arthralgia. The syphilitic lesions become prominent, edematous, and more brilliant in color. The reaction lasts only a few hours and can be controlled by mild sedation. The rash begins to fade within 48 hours and is usually gone by the 14th day. The reaction does not occur after a second injection. Reduction of the initial dose of penicillin does not prevent the Herxheimer reaction. In no case should treatment be withheld or discontinued because of it. Management of a Jarisch-Herxheimer reaction involves effective control of the hyperthermia and the immediate administration of oxygen to the mother.

For patients at high risk for a Jarisch-Herxheimer reaction, the author has given, in a controlled environment, an erythromycin antibiotic the day before administration of the benzathine penicillin in an attempt to avert such a reaction.

It is strongly advocated that gravidas with high VDRLs, secondary syphilis or early latent syphilis have therapy administered in a setting in which hyperthermia and fetal need for supplemental oxygenation can be effectively handled.

ADEQUACY OF CURRENT MATERNAL THERAPY FOR PREVENTION OF CONGENITAL SYPHILIS

During pregnancy, in the absence of appropriate therapy, early untreated syphilis gives rise to significant loss by spontaneous abortion, stillbirth or perinatal demise. Among the survivors of such infected pregnancies, about 40% of the offspring exhibit various stigmata of congenital syphilis.

Therapy of syphilis in pregnancy has been that of syphilis of the non-pregnant woman. The Centers for Disease Control (CDC) recommends 2.4 million units of benzathine penicillin G for the management of early syphilis (disease of less than one year's duration). The clinical study which best focuses on the problem of therapeutic failures is that of Mascola *et al.* In the year 1982, 50 of the 159 cases of congenital syphilis reported to the CDC occurred in Texas. Of the 50 cases analyzed, 39 could have been prevented

by appropriate prenatal care with adequate clinical diagnosis and treatment. Of the remaining 11 cases, seven women were incubating syphilis at the time of delivery and had negative serological results at the time of parturition. What was disturbing was the fact that four women who received the recommended treatment with benzathine penicillin went on to deliver congenitally infected infants. Ricci *et al.* published a series of fifty-six cases of congenital syphilis. In this series, seven of the gravidas were treated during pregnancy. Five received benzathine penicillin G (2.4 million units) and two received erythromycin. Most of the treatment failures occurred after therapy in the second or third trimester. Benzathine penicillin G therapy in these cases failed to eradicate apparently established fetal disease. Like congenital rubella, fetal infection *in utero* is not a time limited event. Fetuses with congenital syphilis have a continued organism-cell interaction such that morbidity is cumulative with time.

Wendel *et al.,* have reported on the impact of maternal therapy with syphilis during pregnancy. Theirs is one of the few studies in the literature which identified the stage of maternal syphilis and in so doing provided some insight as to the actual level of efficacy of maternal therapy on infants with established fetal infection. When pregnant women with secondary syphilis were treated with greater than 2.4 million units of benazthine penicillin G, 5.3% of neonates were born infected.

There have been very few, if any, adequate studies on therapy for syphilis in pregnancy and on the ability of maternally administered antibiotics to eradicate established disease *in utero*. Good demographic and therapeutic studies which analyze the frequency of therapeutic failure for a given stage of maternal disease are lacking. What is known is that penicillin *per se* does not readily traverse the placental barrier. To achieve therapeutic drug levels in amniotic fluid for bacterial disease, it is necessary to 'stack' the maternal-fetal gradient by administering large doses of the antibiotic. Glover and associates were unable to demonstrate the presence of penicillin in amniotic fluid samples of a pregnancy complicated by syphilis twenty hours following the administration of 2.4 million units of benzathine penicillin, and again four days later following a further dose of the drug. The inability of traditional benzathine penicillin therapy (advocated by the CDC) to preclude the occurrence of congenital syphilis may be a partial function of the low levels of penicillin demonstrable in serum after intramuscular injections of 2.4 million units of benzathine penicillin, the difficulty with which penicillin enters the fetal compartment and the dosage required to abort incipient viruses and eradicate established disease.

PROPOSED MATERNAL THERAPY OF SECONDARY SYPHILIS IN PREGNANCY

The major therapeutic considerations in the treatment of gravidas with advanced active disease are:

(1) avoidance of fetal death *in utero;* and
(2) effective eradication of maternal and fetal disease.

Because of the possibility of adverse fetal consequences from the Jarisch-Herxheimer reaction, Monif has

Table 52.4 Alternative therapy advocated for a gravida with secondary syphilis*

	Medication and route	***Rationale***
I.	10 million units of penicillin G (intravenous)	Forty or sixty percent of pregnant patients with secondary syphilis will exhibit a Jarisch-Herxheimer reaction. A comparable phenomenon may occur Involving the placenta, causing acute placental insufficiency and possible abortion. If the reaction occurs, diminish but do not discontinue infusion, administer oxygen and antipyretic drugs; intravenous route of administration is chosen to give better drug control. If no reaction occurs, discontinue intravenous therapy.
II.	2.4 million units of slowly released benzathine penicillin	Standard treatment of the non-pregnant female as advocated by the CDC.
III.	Ampicillin 2 grams q 12 hours ×10 days (oral)	Penicillin traverses the placental barrier poorly. Despite *in utero* treatment with standard therapy, *T. pallidum* may not be eradicated. To treat fetus, as opposed to mother, the placental drug gradient must be stacked. Ampicillin traverses the placental barrier more effectively than penicillin. Replication time for *T.pallidum* is 33–36 hours. Because of non-synchronous replication, the fetus should be treated for a minimum of 7 days.

*The above therapy differs significantly from that advocated by the Center for Disease Control and is not FDA-approved

advocated a policy of initiating penicillin therapy through a controllable vehicle (Table 52.4). Five million units of penicillin G in a liter of five percent dextrose are administered by a slow intravenous drip. If a Jarisch-Herxheimer reaction occurs, the infusion is temporarily discontinued. Oxygen is given by a Venture mask with the patient lying on her left side. Antipyretics are given to maintain the temperature below 38.5ºC. The fetal heart rate is monitored. If non-stress tests remain positive and good fetal heart rate variability persists, the infusion is cautiously reinstated. If evidence of fetal distress is identified, the situation is discussed with the mother and an individualized program of therapy is instituted.

The conversion from intravenous penicillin to oral ampicillin is predicated upon fetal considerations. The difference in lipid solubility and ionic binding between benzathine penicillin and ampicillin is such that ampicillin more readily traverses the placental barrier. The level of penicillin in cord and amniotic fluid is governed by the maternal/fetal gradient. The maternal levels attainable with benzathine penicillin are low and vary from individual to individual.

The use of benzathine penicillin assures compliance and effective maternal therapy which is a cornerstone of public health policy.

Without a collaborative multiple institutional double-blinded comparative study spanning at least a five to ten year period, documentation of the superiority or otherwise of this regimen will be wanting.

CONGENITAL SYPHILIS

Congenital syphilis is primarily a reflection of inadequate prenatal care. In a review of 54 cases of congenital syphilis in the state of Massachusetts, 18 mothers had received no prenatal care, 23 had received inadequate prenatal care, 10 cases resulted from maternal infection or reinfection following initial prenatal examination, and 3 were due to the failure of the physician to obtain the appropriate tests. Now, a significant number of congenital syphilis cases have been identified in which the mother had received adequate maternal therapy during gestation.

Analysis of infant therapeutic failures after maternal treatment for syphilis in pregnancy has documented the significance of proximity to maternal spirochetemia and probably the magnitude of its occurrence. Sheffield *et al.* identified 43 gravidas who had received antepartum therapy for syphilis according to the CDC guidelines and who were delivered of a newborn with congenital syphilis. The majority of these women had been treated for secondary or early latent syphilis. Thirty-five percent of these women were treated within 30 days of delivery. Fifty-six percent of the infants were delivered before 36 weeks and 26% of them were stillborn infants. Similarly, Alexander *et al.* identified that 73% of their treatment failure occurred in women with either secondary or early latent syphilis.

Why did these therapeutic failures occur and is there a relationship of therapy to preterm delivery?

The incidence of occult neonatal infection or disease does not parallel the incidence of syphilis in pregnancy. Maternal therapy given early in the infection is often adequate to eradicate spirochetal replication prior to spirochetemia. If the occurrence of spirochetemia antedates the establishment of pregnancy, the probability of subsequent metastatic spread to the products of conception in the face of an established maternal immune response is non-existent.

Penicillin concentrations as low as 0.018 μg/ml, sustained for seven days, results in nearly 100% treponemacidal activity. Idsoe *et al.* demonstrated that this drug concentration can be achieved with a single dose of 2.4 mU of benzathine penicillin in non-pregnant adults. The physiology of pregnancy alters penicillin pharmacokinetics such that the majority of pregnant women administered a single dose of 2.4 mU of benzathine penicillin do not attain a level of 0.018 μg/ml in fetal blood for the time required to eradicate the organism.

The risk of an adverse fetal/neonatal outcome is theoretically a function of the magnitude of the maternal spirochetemia, the effectiveness and safety of antimicrobial therapy and the magnitude of fetal involvement.

The placenta, like the conceptus, is involved in the disease process. As with organ pathology, the mass of treponema organisms determines the extent of fetal pathology. In its most overt form, syphilitic placentitis is manifested by a marked increase in placental weight such that the placental-fetal weight ratio is in the range of 1:3 or even 1:2. The increase in weight reflects the presence of a dense stroma beneath the chorionic layer of the villus, in which a compensatory increase in the number of vascular channels may be identified. The overall effect is an increase in connective tissue and cellular mass between the maternal and fetal circulation analogous to an alveolar capillary block in the lungs. With advanced disease, placental erythroblastosis may be present.

The chorionic villi show inflammation with proliferative vasculitis, perivasculitis, or endovasculitis. The net effect of these alterations of placental architecture is probably reflected in an alteration of function resulting in low birthweight babies and stillborn infants. Owing to the lengthy division time of *T. pallidum* compared to that of most bacteria, infection of the products of conception does not tend to result in immediate abortion. However, extensive involvement of the fetus may result in its demise prior to parturition.

The demonstration on ultrasonograms of the placenta should alert the clinician to the possibility, if not probability, that with the institution of penicillin therapy, the mother will experience a Jarisch-Herxheimer reaction. The accompanying hyperthermia may be sufficient, when added to an already compromised maternal/fetal exchange, to terminate life.

Congenital syphilis following hematogenous dissemination results in multiple organ involvement, with characteristic lesions occurring in the placenta, lungs, bone marrow, liver, and spleen. Tissue response is markedly similar to that observed in the adult except that parenchymal growth seems to be retarded, a condition that may reflect the predilection for and pathologic effect on small blood vessels. The main histologic features are extensive proliferation of fibrous connective tissue in association with mononuclear cell infiltration and small vessel endothelial proliferation. The principal difference between this pattern and that observed in adult tissues is that plasma cell infiltration, which is so characteristic in adult tissue, is markedly less conspicuous.

Despite the fact that a target organ is the site of spirochetal replication (as demonstrated by appropriate staining techniques), prior to the fifth month of gestation there is an absence of a significant host response to *T. pallidum* by the fetal organs. The absence of morphologic stigmata of infection had provided the basis for the contention that fetal involvement did not occur until the fourth month of gestation. *T. pallidum* does cross the placenta and can involve fetal organs at any time during gestation; however, inflammatory lesions indicative of a host response with plasmacytoid or plasma cells do not occur until the 20th week of gestation in congenital syphilis.

Widespread organ involvement may be responsible for a hemolytic anemia, thrombocytopenia, and hepatosplenomegaly. These manifestations of disease may or may not be associated with cutaneous and mucous membrane lesions. In far advanced cases, the diagnosis may be inferred and documented by placental examination.

Congenital syphilis is rarely diagnosed in the neonatal period. If clinical signs are present at birth, 50% of the infants will die in the neonatal period. In the first month of life fewer than 10% of the cases are identified. That organ pathology is not fullblown at birth emphasizes the necessity for early diagnosis and therapy. Owing to the rising incidence of infection since the 1950s, more and more cases of infection in the terminal stages of gestation will occur and will result in the delivery of infants with no overt manifestation of spirochete replication. The probability of the acquisition of disease between initial serologic surveillance and parturition is approximately 0.6 to 2/1000 live births. It becomes increasingly apparent that in high-risk populations, serologic surveillance at parturition needs to become part of comprehensive prenatal care.

Diagnosis

An infant born to a mother whose pregnancy was complicated with syphilis will have within its intravascular compartment IgG antibody of maternal origin. These antibodies quantitatively and qualitatively may mask a fetal response to infection, which is predominantly IgM in character. The cord VDRL and FTA-ABS titers correspond to those determined for the maternal serum. If intrauterine infection has occurred, cord blood or neonatal serum will contain a composite of IgG of maternal derivation and endogenous fetal IgM. If the infant is born at term, the VDRL titer tends to be slightly higher than the maternal value. Since maternal IgM does not cross the placenta, the detection of specific IgM in cord or newborn serum indicates that there has been exposure *in utero* of the developing embryo or fetus to the antigenic determinants of *T. pallidum*. Depending on the severity and duration of the disease, IgM levels within cord or neonatal serum may be markedly elevated above the anticipated value. Congenital infection can be documented by the IgM FTA-ABS test or IgM immunoblots. Cardiolipin tests, such as the VDRL test and the usual treponemal test, are of little value in the diagnosis of congenital syphilis. The application of the IgM FTA-ABS test may be useful for the identification of congenital syphilis in infants who have few or no symptoms at birth, or for confirmation of the diagnosis in the more overt form. Because both false-positive and false-negative results have been reported with the IgM FTA-ABS test, serial follow-up is still indicated when non-specific IgM antibodies are demonstrable in the cord serum of a neonate born of a seropositive gravida. Low levels of IgM specific for *T. pallidum* may be present at birth—even though the mother may have received adequate treatment—and represent a serologic scar similar to that of the FTA in the adult. Children born of a seropositive mother must be periodically monitored for as long as 3 months for FTA-IgM antibody in order to exclude the possibility of delayed onset of infection.

An under utilized means of confirming congenital syphilis is the application of PCR testing directly to placental tissues. This application is particularly applicable to the establishment of a diagnosis in stillborn fetuses.

At birth, neonates with congenital syphilis may present a spectrum from full blown syndrome to a normal appearing infant. Forme fruste of the disease may present with unexplained hepatomegaly, usually associated with anemia.

Therapy

Infants with congenital syphilis should have a CSF examination before treatment, since the findings will influence therapy. If the CSF is abnormal, the neonate should receive either aqueous crystalline penicillin G 50000 units/kg IM daily for a minimum of 10 days. If the infant's CSF is normal, a single dose of benzathine penicillin G 50000 units/kg IM suffices. Other antibiotics are not recommended for neonatal congenital syphilis. In the more severely affected newborn infants, a Herxheimer reaction often occurs in the course of penicillin therapy. Infected neonates may be seronegative if maternal infection occurred late in gestation. Infants should be treated at birth if maternal treatment was inadequate or unknown, if drugs other than penicillin were given, or if adequate follow-up of the infant cannot be ensured.

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53
Entamoeba histolytica (amebiasis)

Entamoeba histolytica is a pseudopod-forming non-flagellate protozoan parasite. Based on isoenzyme analysis, typing by monoclonal antibodies to surface antigens and restriction length polymorphism, *E. histolytica* has been reclassified into two species which are morphologically identical: *E. histolytica,* an invasive disease-causing organism and *E. dispar*, a non-invasive parasite.

The subspherical cyst form of *E. histolytica* ranges from 10 to 20 nm in diameter and is surrounded by a hyaline-like cyst wall. This form of the organism is present only within the lumen of the colon and in the feces. It is uninucleated and contains within its cytoplasm a large glycogen vacuole and chromatoidal bodies. The cyst undergoes binary fissions, resulting ultimately in a quadrinucleated cyst. With the series of divisions, the chromatoidal bodies and glycogen vacuole are lost. The morphologic diagnosis of amebiasis often rests on the identification of the quadrinucleated cyst form. *E. histolytica* undergoes distinct morphologic alterations during its natural life cycle within the gastrointestinal tract.

Dissemination of the organism and infection are due to ingestion of contaminated water, vegetables, or other food containing the cyst form. Asymptomatic cyst passers comprise the main reservoir for infection and disease. Cysts may remain viable for months in an appropriate moist environment. It is probable that dirt and houseflies are important intermediaries in the dissemination of the organism.

The active trophozoites are liberated by enzymatic digestion of the cyst wall within the small intestine. Organism replication is optimal under anaerobic conditions. Bacterial multiplication, by reducing the oxidation-reduction potential within areas of fecal stasis, creates an environment favorable for *E. histolytica*. Consequently, the concentrations of trophozoites are greatest at sites of maximum fecal stasis, such as the cecum, sigmoid colon, and rectum. The sites of mucosal invasion parallel the sites of greatest concentration of the organism.

The amebic trophozoites are present at the sites of tissue invasion as well as within feces. Trophozoites are characterized by granular cytoplasm in which phagocytized red blood cells can frequently be demonstrated. The erythrophagocytosis by the trophozoites is deemed a pathognomonic characteristic of *E. histolytica*.

The incidence of *E. histolytica* in a given population depends on the sources of contamination and the hygienic standards governing the environment. Infection is predominantly asymptomatic (90–99%). Only a small percentage of individuals harboring the organism experience an acute diarrheal syndrome characterized by cyclical bouts of diarrhea and constipation or, occasionally, bloody diarrhea associated with colicky abdominal pains. Most individuals eliminate the organism from the gut in 12 months.

The tissue invasiveness of the trophozoites is reflected in the organism's ability to produce ulcerated lesions associated with extensive undermining of the mucosal margins,

resulting in a flask-shaped submucosal abscess. Pathogenic *E. histolytica* exerts a lytic effect on tissue. Nevertheless, unless secondary bacterial infection occurs, there is a relative paucity of an inflammatory response in the adjacent tissue. Precysts are formed as the trophozoites migrate toward the rectum.

Extraintestinal infection occurs. The prime target organs are liver, lung, brain, and spleen. The major organ of extraintestinal infection is by and large the liver. It is thought that microemboli containing trophozites may occur as the result of thrombosis of vessels in the submucosa, particularly of the ileum. The microemboli are carried to the liver by the portal circulation. Cerebral abscesses are rare, are almost always associated with hepatic involvement, and are thought to be due to hematogenous spread.

Approximately 4% of patients with clinically overt amebiasis develop extraintestinal complications; however, the true incidence of amebic hepatic abscesses exceeds this figure. In endemic areas, more than 50% of patients with hepatic involvement give no history of amebic diarrhea or dysentery and have no demonstrable amebae in the feces.

The ability of *E. histolytica* to adhere to epithelial cells appears to be a prerequisite for disease. Amebic adherence to mammalian cells and human erythrocytes *in vitro* appears to be mediated by at least two amebic receptors. Amebic microfilament function and possibly intracellular calcium flux are necessary for adherence to occur. Amebae are able to lyse target cells only after adherence has occurred. Cytolysis requires intact amebic microfilament and calcium flux to function.

Host factors such as age, species specificity, bacterial flora, nutrition, iron availability, and cholesterol levels may be relevant to occurrence of disease. High-carbohydrate, low-protein diets produce more severe amebiasis in laboratory animals. A high incidence of amebic dysentery as well as extraintestinal amebiasis is documented in populations subsisting on diets of this nature.

In the United States, women at greatest risk for developing clinically overt amebiasis are immigrants from and travelers to countries where infection is endemic. Infection usually manifests within a year of immigration to the United States. Travelers returning from endemic areas are at a low but definite risk of acquiring amebic infection. In a study of 2700 German citizens returning from tropical areas, Weinke *et al.* documented a 4% incidence of *E. histolytica/E. dispar* infection. Diarrhea occurred in 80% of travelers with *E. histolytica*. Only 5% of travelers with diarrhea and amebic infection had *E. dispar* infection.

AMEBIASIS AND PREGNANCY

Malnutrition and the immunosuppression of pregnancy may convert asymptomatic intestinal or vaginal carriage into clinically overt disease or magnify the resultant morbidity of disease. Amebiasis occurring in a gravida tends to be more severe and is associated with a higher incidence of complications. Abioye noted that 68% of fatal cases of amebiasis in females occurred in association with pregnancy. On the other hand, only 17.1% of fatal typhoid cases and 12.5% of other fatal enterocolitis cases among females occurred during pregnancy. Czeizel *et al.*, noted that women with spontaneous abortions had a significantly higher incidence of positive stool cultures for *E. histolytica,* as compared to women having term births.

As a rule, more severe disease is seen in the very young and old, the malnourished, and pregnant women.

FEMALE GENITAL TRACT INVOLVEMENT

Two syndromes that can be attributed to *E. histolytica* are encountered in the non-pregnant female and involve the female genital tract. They are:

(1) amebic vulvovaginitis;
(2) amebic vulvar ulcers (cutaneous amebiasis);

Although extraintestinal amebiasis is thought to be caused by blood-borne microemboli from the intestines, involvement of the female genital tract is more likely due to metastatic mechanical spread from feces or anorectal involvement, or both. Characteristically, the patient complains of a serosanguinous or seropurulent vaginal discharge, soreness of the vagina, and dyspareunia. The character of the vaginal discharge may be so sanguinous that a patient complains of menstruating every day or, in postmenopausal women, of recurrence of menses.

Amebic penetration of the vaginal mucosa is associated with cell necrosis. In general, the edge of the resultant ulcer is relatively shallow compared to those in the gastrointestinal tract. Secondary bacterial infection is primarily responsible for purulent sloughing of the overlying mucosa and severe inflammatory reactions in the submucosa.

Colonization or mild diarrhea with *E. dispar* rarely requires medical intervention as these amebia have not been identified as the etiology of colitis or hepatic abscess. In contrast, women colonized by *E. histolytica* are at risk months and even possibly years later for the development of invasive disease.

DIAGNOSIS

Patients with amebic colitis characteristically present with a history over several weeks of gradual abdominal pain and diarrhea which may be overtly bloody. Fever is present in the minority of patients with amebic colitis and absent in women with vulvovaginal disease.

The initial diagnostic dilemma is distinguishing diarrhea that contains blood due to amebiasis from that caused by *Shigella, Salmonella, Campylobacter,* and enteroinvasive and enterohemorrhagic *Escherichia coli*. The diagnosis of amebic colitis may be difficult as the presentation may be insidious. Bleeding may occur without diarrhea. Fever is an unusual finding. A single stool examination for parasites is insensitive. Histologic confirmation of infection on a biopsy specimen may miss a diagnostic lesion.

The diagnosis of intestinal amebiasis is made by identifying either trophozoites or cysts in vaginal discharge or ulcer exudate. Only the trophozoites are present in exudate. Scraping of the ulcer edge or of discharge should be examined for motile erythrocyte-containing amebae by direct mount in saline on a warm microscope stage. The characteristic motility is that of a directed, linear movement across the microscope stage. Microscopic examination is not species specific. Erythrophagocytic amebia are more likely to be *E. histolytica* than *E. dispar*.

In biopsy material stained with conventional hematoxylin and eosin, the amebae are not readily identifiable except by experienced viewers. It is necessary to utilize periodic acid-Schiff stain, which causes the amoebae to stand out as bright red rounded bodies.

Because a single stool examination identifies only one-third of infected patients, at least three specimens should be examined for amebic cysts and trophozoites before excluding the diagnosis of amoebiasis.

The diagnostic gold standard is culture confirmation with isoenzyme analysis. Advances in technology (strain-specific DNA probes and polymerase chain reaction, PCR) have made direct detection of *E. histolytica* antigens in serum and feces possible. Using enzyme-linked immunosorbent assay (ELISA) or epitope-specific monoclonal antibodies, one can further differentiate non-pathogenic from pathogenic *E. histolytica*. Demonstration of galactose adhesion in serum is highly specific for infection by pathogenic *E. histolytica*. PCR and antigen detection tests have comparable sensitivities, identifying approximately 85% of *E. histolytica* identified by the gold standard.

A multiplicity of serologic tests exist for diagnosis of amebiasis. These include complement fixation, agar gel precipitation, indirect hemagglutination (IHA), counterimmunoelectrophoresis (CIE), and gel diffusion. Serological tests for *E. histolytica* tend to remain positive for years after initial infection. These may be of limited value in distinguishing current disease from a prior invasive event. Eighty-five percent of patients with biopsyproven invasive intestinal amebiasis have a positive serologic study by various techniques.

The elevation of the IHA titer does not correlate with severity of disease. IHA titer remains elevated (>128) for years following invasive disease. Other serological tests such as CIE and gel diffusion precipitin test become negative after approximately six months and can therefore be helpful in diagnosis of recurrent or active disease in a patient from an area endemic for amebiasis. The prime value of serologic testing is in enhancing or supporting a tentative diagnosis of extraintestinal (hepatic) amebiasis.

The organism can be grown on selective media and in tissue cultures; however, such procedures usually are not warranted in conventional cases of amebic vulvovaginitis or cutaneous ulcer. Whenever *E. histolytica* is identified, the possibility of amoebic complications must be ruled out.

THERAPY

The key to therapy is the eradication of the intestinal reservoir of the organism. Local lesions will respond to systemic therapy for amebiasis. Drug therapy for genital involvement is contingent on the extent of the disease

Table 53.1 Drug therapy For *Entamoeba histolytica*

Clinical setting	***Drug of choice***	***Adult dosage***
Asymptomatic	Metronidazole plus diloxanide or paromomycin	750 mg tid×10 days 500 mg tid×10 days 30 mg/kg/day in three divided doses ×10 days

Moderate to severe Intestinal or vulvovaginal disease	metronidazole	750 mg tid×10 days or 2.4 g qid ×2–3 days
	or tetracycline plus chloroquine (base)	250 mg qid×15 days 600 mg, 300 mg then 150 mg×14 days

process elsewhere. Metronidazole (Flagyl) is the drug of choice for amebiasis (Table 53.1).

Colonization with *E. histolytica* can be treated with a luminal agent alone. Drugs effective against uncomplicated gastrointestinal infection include paromomycin and iodoquinol. The recommended duration of administration with paromomycin is 7–10 days and with iodoquinol 20 days. Paromomycin, 500 mg tid has the advantage in pregnancy of being better tolerated.

Cure rates as high as 92% have been achieved. Sigmoidoscopic studies indicate that trophozoites are no longer in the feces, and the ulcers heal by the end of the fifth or sixth day of treatment. Because therapy is only 90–95% effective, follow-up cultures of both genital sites of infection and stool are warranted.

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Plasmodial infections (malaria)

Malarial infection in man results from the bite of an infected female Anopheles mosquito in which the sporogonic cycle of development of the malarial parasite has taken place. Schizogony, or the asexual cycle (Figure 54.1), begins within the parenchymal cells of the liver. The exo-erythrocytic cycles within the liver result in the production of merozoites. This form of the malarial parasite then enters into red blood cells where it develops and multiplies asexually. This is termed the schizogonic erythrocytic cycle. The end product is the production of a new crop of merozoites, which are released through rupture from the cells and recommence the cycle. During the erythrocytic cycle a few parasites become differentiated into male and female gametocytes which are now present within the intravascular compartment awaiting ingestion by blood-sucking female Anopheles mosquitoes to complete their life cycle. Within the mosquitoes, fertilization occurs, with the production of the zygote. The zygote then undergoes successive stages of differentiation into an ookinete, which then penetrates the stomach wall of the mosquito to form an oocyst. From the mature oocyst sporozoites are liberated; these ultimately migrate to and reside within the salivary gland of the mosquito. They are then injected with the saliva into the human host at the time of a blood meal.

Four different species of Plasmodium infect man: *Plasmodium vivax, P. ovale, P. malariae*, and *P. falciparum*. While basically similar in their life cycles, they differ significantly in pathogenic potential, relapse rate, chronicity, and development of resistance to drugs.

IMMUNOLOGY OF INFECTION

An understanding of female genital tract involvement by malaria is almost inseparable from an understanding of the immunology of infection. Plasmodial infection, owing to an intravascular cycle and access to the reticuloendothelial (RE) system, represents an intense form of antigenic stimulation. Marked immunoglobulin synthesis occurs, resulting in greatly increased levels of serum immunoglobulins. Shortly after parasitemia appears, there is a marked increase in IgG, IgM, and IgA antibodies, IgG rising to the highest levels and persisting the longest. The end result is a hypergammaglobulinema, the major component of which is IgG. Only 1–5% of the IgG appears to be specific antibodies. IgG and IgM antibodies, principally the former, can afford some protection apparently, mainly against the merozoite stage of the parasite.

Immunity to infection ususally requires repeated exposure to the parasite to become longlasting. The malarial organisms have the ability to vary major target antigens. Antibody-dependent immunity is mediated primarily by cytophilic IgG antibodies which activate cytotoxic and phagocytic effector functions of neutrophils and monocytes. Malarial infection also results in the production of IgE specific antibodies. IgE immune complexes, by crosslinking IgE receptors on monocytes, elicit a local overproduction of

tumor necrosis factor (TNF). Elevated production of TNF is associated with increased risk of severe disease and death due to *Plasmodium falciparum* infection.

The major cells controlling blood stage infection are the Th1 and Th2 subsets of CD4 cells. Interferon-gamma production plays a key role in anti-malarial defense.

Antibodies to the malarial parasites tend to be at least species- and strain-specific. This can be strongly inferred from clinical studies. The administration of 2.5 g hyperimmune gamma-globulin to children results in both a dramatic drop in parasitemia and, within one week, progressive regulation of disease. This phenomenon is not

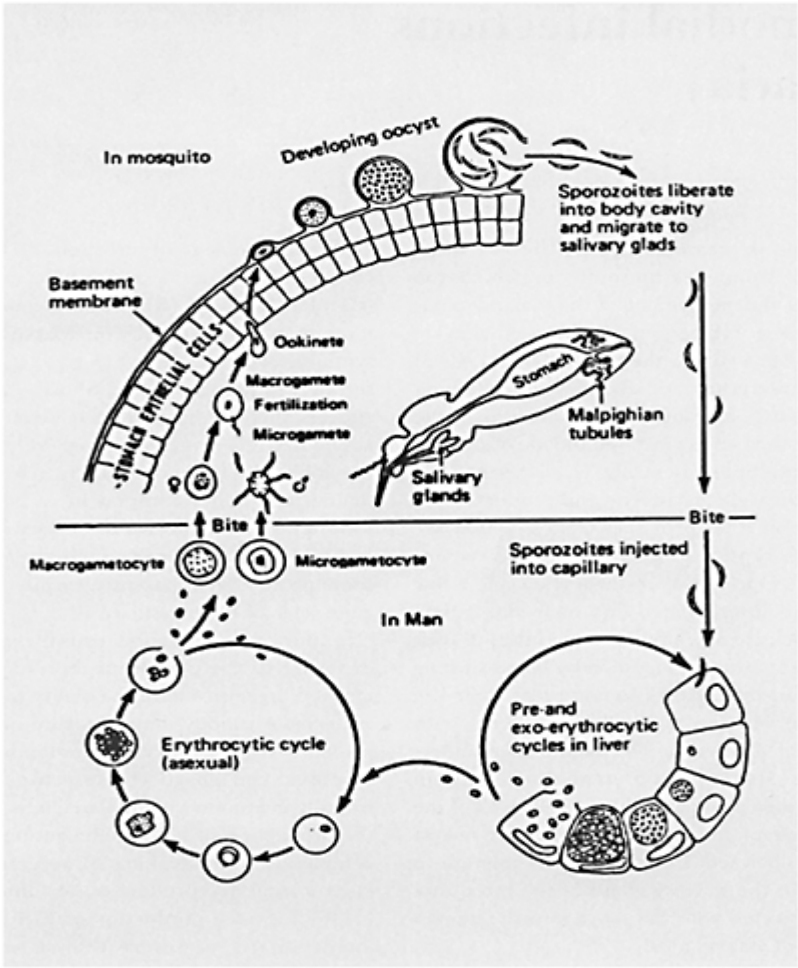

Figure 54.1 Life cycle of Plasmodium vivax (Adam MG. In *Medical and Veterinary Protozoology*. Edinburgh: Livingstone, 1971:89)

observed with non-immune gamma-globulin nor with that prepared from an endemic area where different strains of plasmodium predominate. The effectiveness of passively acquired specific antibody from mother to fetus also suggests the importance of humoral immunity. Even when parasitemia occurs at birth, its clinical expression is suppressed.

Parasitemia results in hypertrophy of the RE system, as reflected by hepatosplenomegaly and by bone marrow alterations. The importance of this, as can be shown experimentally, is that non-specific activation of phagocytosis can greatly increase the rate of parasitic removal. The importance of the RE system in controlling erythrocytic infection can be inferred from the effects of splenectomy which, in essence, constitutes a significant reduction in the size of the RE pool. Splenectomy decreases immunity to all malarial parasites and may result in relapse and recrudescence of infection.

Phagocytosis of the parasites is often opsonin mediated. The antigens on the surface of the parasitized erythrocytes are important in terms of opsonization and phagocytosis of infected erythrocytes. Destruction of the parasite is predicated on intracellular digestion by macrophage elements. The immune destruction of red blood cells may produce a serious folic acid deficiency which not infrequently is superimposed on a microcytic hypochromic iron-deficiency anemia.

The majority of malaria cases diagnosed in the United States are imported from regions in the world where malaria transmission is known to occur. However, each year congenital infection and infection resulting from exposure to blood or blood products are reported in the United States. In rare instances, infection has occurred through local mosquito-borne transmission. More than 80% of imported malaria cases occurred in persons who were either not taking or taking non-recommended chemoprophylaxis.

MALARIA IN PREGNANCY

Malaria in pregnancy occurs primarily in endemic areas. Nevertheless, the recent resettling of refugees from Southeast Asia has provided a setting in which plasmodial infection could conceivably have an impact on a civilian population because of either secondary spread in areas with potential vectors (Anopheles mosquitoes) or transfusion-induced infection. These possibilities underscore the need for a greater awareness and knowledge about plasmodial infection.

Malaria is said to be exacerbated by pregnancy. Women with little or no immunological experience with the parasite prior to the first pregnancy are particularly vulnerable to infection. Parasites have been shown to adhere to the surface of the trophoblastic villi, eliciting local inflammation and necrosis of adjacent placental tissue. Histologically, placental malaria is chararacterized by the presence of parasites and leucocytes within the intervillous spaces, proliferation of cytotrophoblastic cells and thickening of trophoblastic basement membrane. In holoendemic areas, both placental infection and poor pregnancy outcomes decrease in frequency with successive pregnancies.

It has long been noted that women residing in areas endemic for malaria appear to lose some of their acquired resistance during pregnancy and may experience severe malarial attacks. A theoretic basis for this clinical impression seems to exist. For many strains of *P. falciparum,* maturation of the schizonts occurs within the bloodstream in what are

termed ‘internal organs’ or ‘deep sinuses’, for example, the spleen. Sequestration results from adhesive interaction between parasite-derived proteins expressed on the surface of red blood cells and host molecules on the surface of endothelial and cytotrophoblastic cells. Parasite-encoded adhesion molecules prevent circulation of parasitized erythrocytes. The maternal vascular compartment within the placenta constitutes an additional site for parasitic replication. The greatest degree of placental infestation is observed in highly immune patients. While maternal symptomatology is relatively mild, fetal wastage is disproportionately increased. Experimental data tend to point to a decreased maternal response in terms of cellular immunity and a possible decrease in RE system clearance during pregnancy. Should such data be applicable and substantiated in human subjects, they might provide a partial mechanism for the clinical deterioration observed in pregnancy.

Severe attacks of malaria not infrequently result in second-trimester abortion, intrauterine death with macerated stillbirths, fresh stillbirths due to intrapartum asphyxia, or premature labor and delivery. The predominantly hypochromic microcytic anemia caused by the plasmodial organisms may be of sufficient severity to induce congestive heart failure. If the disease remains untreated, both maternal and fetal demise may occur. In hyperendemic areas, gravidas may exhibit severe anemia and marked hepatosplenomegaly at the time of parturition. The enlarged spleen may protrude into the pelvis and, on a mechanical basis, cause dystocia.

CONGENITAL MALARIA

Detectable malarial parasitemia in newborn babies from areas highly endemic for malaria is strikingly rare. In contrast, infants from non-indigenous infected mothers may have clinically overt congenital malaria. The importance of passive transfer of immunity is suggested by the initial rarity of disease in neonates and infants in an endemic area. Congenital malaria is exceptional in babies of immune mothers, even though the placenta is not infrequently—and sometimes heavily—infected. With increasing degrees of immunity to malaria, the frequency of placental infection rises. The intervillous space in the placenta may be packed with parasitized cells and macrophages. The more severe the infestation, the worse the parasitization of the placenta and the greater the patient’s immunity. Well-immunized patients can have minimal clinical symptoms of malaria but have significant fetal wastage. Placental infection with *P. falciparum* is associated with low-birthweight babies on the presumed basis of impaired placental circulation.

The relatively common occurrence of congenital malaria in babies born to non-immune but infected mothers indicates that in the majority of cases the parasites often attain access *in utero* to the fetal circulation. It is presumed that the levels of specific protective maternally-derived antibodies prevent parasitic multiplication. Even when parasitemia is present at birth, the disease process is usually not manifested until the second or third month, at a time when the bulk of maternally-acquired specific antibodies has undergone degradative elimination.

DIAGNOSIS

The signs and symptoms of malaria are variable. The majority of patients present with fever. Other common symptoms include headache, back pain, chills, increased sweating, myalgia, nausea, vomiting, diarrhea and cough. Malaria needs to be included in the differential diagnosis of illness in a febrile person with a recent history of travel to a malarious area. Clinicans should ask febrile patients for a travel history, particularly when evaluating febrile illnesses in international visitors, immigrants, refugees, migrant laborers and international travelers.

The presence of detectable parasitemia almost always accompanies a clinical malaria attack; however, parasitemia may occur in the absence of significant symptoms.

The diagnosis of acute, active malaria is based on the identification of asexual stages in the erythrocytes. Diagnosis of acute malaria depends on the identification of the parasites in the peripheral blood or in bone marrow. Usually when the organisms are not readily demonstrable in the blood, bone marrow examination is also likely to be unproductive.

Demonstration of gametocytes, while confirming malarial infection, is not diagnostic of acute infection. Gametocytes may be found in the peripheral blood weeks and even months after an overt attack has subsided or been cured.

Both a thick and thin blood smear should be made. The thick blood smear is made by touching a drop of blood with a clean slide. Using the corner of another slide, spread the blood drop into the shape of a circle or a square of about one centimeter square. Gently squeeze the patient's finger again and touch the end of a clean slide to the newly formed drop of blood. Take this slide and hold the edge that has the drop of blood at a 45 degree angle against the surface of the first slide. Wait until the blood has completely spread along the edge of the second slide. While holding the second slide at the same angle, rapidly and smoothly push the slide forward to make the thin smear. Air dry the thin film slide, fix it with methyl alcohol, and stain with Giemsa's stain. Plasmodium parasites are always intracellular. If properly stained, they appear with blue cytoplasm with a red chromatin dot.

Persons suspected of having malaria but whose blood smears do not show the presence of the parasite should have blood smears repeated every 12–24 hours for three consecutive days. The numbers of parasites in peripheral blood smears may vary significantly during a given day. Consequently, repeated examination may be necessary to establish the diagnosis of active malaria.

As a rule, all stages of the erythrocytic cycle can be found in peripheral blood smears of subjects with active vivax, malariae, and ovale malaria. Only the ring forms

Table 54.1 CDC sources for malaria prophylaxis and treatment recommendations

Type of information	***Source***	***Contact***
Prophylaxis	CDC Traveler's Health Voice Information System	877-394-8747
Prophylaxis	CDC's Traveler's Health Fascimile	888-232-3299
Prophylaxis	CDC Traveler's Health Internet Home page	www.cdc.tgov/travel/
Prophylaxis	*Health Information for International Travel*	770-488-7788
Treatment	CDC Malaria Epidemiology Branch	770-488-7788 (8am to 4:30pm, M-F)
Treatment (After hours)	CDC Malaria Epidemiology Branch	404-639-2888 (Request operator page person on call, Malaria Epidemiology Branch)

usually occur in falciparum malaria during the first 10 days of the clinical attack. If no parasites are found on the thin film, wait until the thick film is dry and examine it for organisms that might not have been detected on the thin film preparation.

THERAPY

Since the clinical manifestations of acute malaria are the consequence of the erythrocytic cycle of the parasite, therapy is directed at eradicating this phase of infection. Drugs that destroy the erythrocytic forms of the parasites are termed schizonticides. They include 4-aminoquinolines, quinine, chloroguanide (proguanil), and pyrimethamine. Of these, only the 4-aminoquinolines are commonly used. To achieve a radical cure in *P. vivax, P. ovale,* and *P. malariae* infections, chloroquine must be combined with an 8-aminoquinoline such as primaquine. The destruction of the persistent exoerythrocytic parasites in the liver is achieved only by the latter group of drugs, the 8-aminoquinolines. The Centers for Disease Control (CDC) sources for malaria prophylaxis and treatment recommendations are listed in Table 54.1.

The patient receiving primaquine should ideally be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency to avoid the possibility of hemolysis in susceptible individuals. The drug is given to destroy the exoerythrocytic forms of the parasite which persist within the parenchymal cells of the liver and from which the relapse-provoking parasites emerge. If the enzymatic deficiency cannot be tested for, it is suggested that patients receive a dose one-quarter of that normally administered and be closely observed.

The choice of chemotherapy is influenced by three considerations, including the species of Plasmodium, the immunologic status of the individual, and the susceptibility or

resistance of the infecting parasite to antimalarial therapy. Chloroquine-resistance of *P. falciparum* is a significant therapeutic problem. In *P. falciparum* infections, eradication of the erythrocytic cycle is the prime objective of therapy. In the relapsing malarias, eradication of both the erythrocytic and exoerythrocytic cycles necessitates individualized therapy.

Some of the prophylactic drugs have been shown to alter glutathione levels and in so doing may exacerbate the oxidation-reduction potential attendant in HIV infection. The potential for antimalarial agents to cause problems when combined with other drugs needs careful evaluation.

Severe *Plasmodium falciparum* infection

Complicated *P. falciparum* infection is a medical emergency and requires aggressive medical care. An essential component of the management of severe *P. falciparum* infection is the prompt administration of a rapidly acting drug that kills the asexual erythrocytic stages of the parasite (a schizonticidal drug). Equally important is counteracting the presence of significant anemia.

Parenteral quinine dihydrochloride had long been regarded as the most effective drug for *P. falciparum* infection. Because parenteral quinine is not commercially available in the United States, the CDC Drug Service had provided this drug as a service to licensed US physicians. Recently, the CDC Drug Service has discontinued this policy and advocated the use of quinidine gluconate.

Quinidine, the dextrorotatory diastereoisomer of quinine, is widely available in the United States as parenteral quinidine gluconate. It is primarily used as a treatment of persons with cardiac arrhythmias; however, it has also long been recognized as a potent antimalarial. On an equimolar basis, quinidine is a more active antimalarial than quinine for *P. falciparum*.

The World Health Organization has recommended that an individual with malaria should be treated parenterally if (1) vomiting is prominent and oral fluids and medication are not retained, (2) there are signs or symptoms of neurologic dysfunction, or (3) the peripheral asexual parasitemia is at a level of >5% of erythrocytes infected.

Quinidine administered by slow intravenous infusion is generally well-tolerated, even by critically ill patients, individuals with underlying cardiac disease, and children. Close attention to electrocardiographic changes, such as prolongation of the QT-interval and widening of the QRS complex, may be an accurate indicator of both plasma concentration and incipient cardiotoxicity. Continuous-infusion quinidine gluconate produces effective drug concentrations. A loading dose of 10 mg of quinidine gluconate (equivalent to 6.2 mg of quinidine base)/kg of body weight is given over 1–2 hours, followed by a constant infusion of 0.02 mg of quinidine gluconate/kg/minute. Plasma quinidine levels>6 mg/ml, QT interval>0.6 S, or QRS widening beyond 25% of baseline are indications for slowing infusion rates.

Persons with hypoglycemia, which may be a manifestation of *P. falciparum* malaria and which is exacerbated by quinine/quinidine-induced hyperinsulinemia, should be treated with intravenous dextrose.

Parenteral therapy should continue until parasitemia is <1% (generally, within 48 hours) and/or until oral medication can be tolerated. When patients with cerebral malaria

are treated, clinical improvement is usually observed within 72 hours. If improvement does not occur, drug resistance or inadequate drug delivery, complications of malaria, or other etiologies for the illness should be investigated. Treatment is continued (usually with oral quinine) for a total of 3–7 days, depending on the geographic origin of the infecting parasite.

The course of the parasitemia must be assessed at 12 hour intervals. Failure to reduce parasitemia in the first 24 to 48 hours of treatment should raise the possibility of parasitic resistance to that treatment. No sexual parasite should be detectable on smears four to five days after the course of chloroquine is completed. Persistence after the fifth day indicates drug failure. Gametocytes may persist in the blood for weeks after asexual forms have been successfully eliminated; however, these gametocytes do not cause disease. Their presence should not be indicative of partial treatment failure.

In the non-immune subject who is unlikely to be re-exposed, the objective of therapy may be complete parasitic eradication. In patients in endemic areas, the goal of therapy is to suppress rather than to eradicate infection. Complete eradication would lead to a loss of immunity and probably reinfection. In general, chemotherapeutic agents are administered orally. The parenteral route is indicated only when oral administration is impossible or when parasitemia is severe and rapid control is essential.

MALARIA PROPHYLAXIS

Chemoprophylaxis against malaria in pregnancy has included chloroquine, mefloquine, proguanil, pyrimethamine and pyrimethamine-sulfadone. Use of these agents has been based primarily on risk-benefit criteria.

CDC recommends mefloquine (Lariam) alone as the drug of choice for malaria prevention for non-immune travelers to areas with drug-resistant *P. falciparum* malaria. Based on accumulating experience with this drug, the prophylactic dosing regimen has been revised to a single dose of mefloquine to be taken every week. The first dose should be taken one week before travel. It should be continued weekly during the entire period of travel in malarious areas and for four weeks after departure from such areas.

Mefloquine is well tolerated when used for prophylaxis. No serious adverse reactions to mefloquine prophylaxis (i.e. psychoses and convulsions) have been observed among persons enrolled in most prophylactic drug trials and surveys of travelers who were taking mefloquine weekly. However, serious adverse reactions have been reported, especially when mefloquine was used for treatment of patients with malaria. The drug is not recommended for use by travelers with known hypersensitivity to mefloquine; pregnant women; travelers using beta blockers; travelers involved in tasks requiring fine coordination and spatial discrimination, such as airplane pilots; and travelers with histories of epilepsy or psychiatric disorder.

Travelers to areas of risk where chloroquine-resistant *P. falciparum* is endemic and for whom mefloquine is contraindicated may elect to use daily doxycycline alone or chloroquine alone. If chloroquine is used, the traveler needs to be aware of the need to seek medical attention for febrile episodes and to carry a treatment dose of pyrimethamine-sulfadoxine (Fansidar®) to be used if medical care is not available within

24 hours. Because of the ever changing guideline, consultation can be obtained from CDC's Malaria Branch, Division of Parasitic Diseases, Center for Infectious Diseases.

The use of doxycycline in pregnancy is contraindicated owing to potential induction of thalidomide-like anomalies if given in the period of osseous organogenesis or subsequent adverse impact on bone and dental development.

Malarial chemoprophylaxis with chloroquine phosphate during pregnancy presents the problem of potential embryopathy. Retinopathy, auditory nerve injury, and central nervous system disturbances have been noted with the use of chloroquine. Hart and Nauton reported on a patient who had taken excessive amounts of chloroquine during four of her seven pregnancies. One pregnancy terminated in miscarriage at 4 months. The remaining three pregnancies resulted in two children with evidence of eighth nerve damage. One child had concomitant posterior column disease and was severely mentally retarded. The remaining child had neonatal convulsions.

While Fansidar® also presents theoretical problems, the drug has yet to be shown to be teratogenic in humans. At the time of parturition, sulfonamides may increase the risk of hyperbilirubinemic neonates because of displacement of unconjugated bilirubin from albumin. Short-acting sulfonamides should not be used close to term. Reinstitution of their use is contraindicated in a nursing mother.

Despite the potential induction of an embryopathy, combined maternal and fetal considerations may argue for chloroquine prophylaxis for gravidas visiting malarial endemic areas. The suggested prophylactic dose is 500 mg chloroquine phosphate (300 mg chloroquine base) orally once a week. Medication should be initiated one week prior to entry into the endemic area and continued for 6 weeks after departure. Nursing infants are thought to develop adequate drug levels provided the mother is on full-dose chemoprophylaxis.

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55
Toxoplasma gondii (toxoplasmosis)

Toxoplasma gondii derives its specific name from the gondii, a North African rodent from which this protozoon was first isolated in 1908. The organism's distribution is ubiquitous. *T. gondii* possesses the capacity to traverse species lines and establish infection not only in man's domestic animals, but in man himself.

Toxoplasma exists in nature in three forms, the trophozoite, the cyst and the oocyst. The most important mode of transmission of infection to man is through the ingestion of poorly cooked meat containing encysted organisms. While the trophozoitic form of the protozoon is particularly sensitive to enzymatic digestion, the encysted form can survive trypsin or acidpepsin for prolonged periods. The presence of viable organisms within striated muscle has incriminated meat as the prime mode of dissemination among carnivores but failed to explain the widespread prevalence in herbivores. The oocysts are the probable mechanism for dissemination of infection to sheep, horses and cattle. Carnivores like cats will excrete oocysts in their feces for two to three weeks following acute infection (Figure 55.1). Once excreted, the oocysts undergo further maturation for three to four days after which they are infectious and in warm moist soil may remain infectious for more than one year. Human or animal contact with soil, grass or other objects contaminated with oocysts and subsequent gastrointestinal processing results in an additional mode of dissemination. Flies can contaminate food with viable oocysts for up to 48 hours after contact with cat feces.

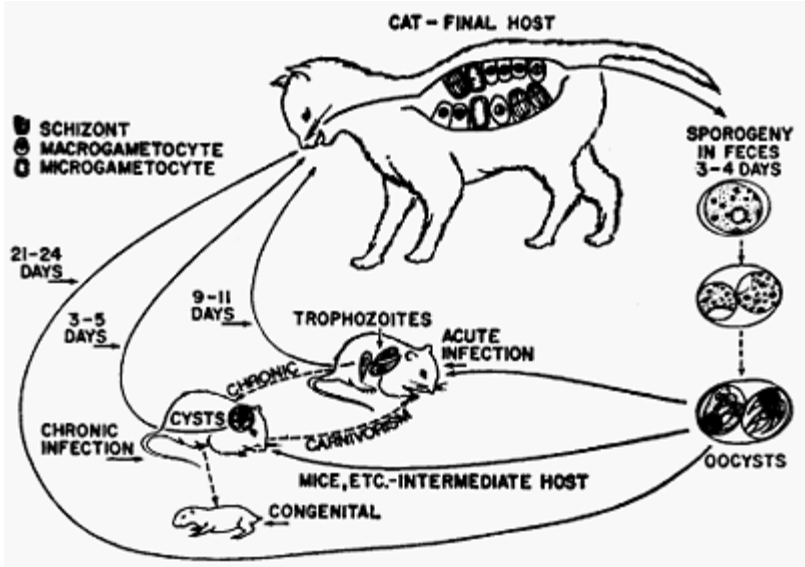
A susceptible cat devoid of antibodies to *T. gondii* will become infected after ingestion of food containing encysted organisms and will excrete oocysts for several weeks. Approximately 50% of felines subsequently challenged by cyst feeding will again excrete oocysts, indicating the probability that a cat may be infectious several times during a lifetime. Those cats that hunt or eat raw meat by contaminating their environment by fecal excretion of oocysts may constitute a potential hazard to gravidas.

MATERNAL INFECTION

Approximately 20–25% of women of childbearing age in the United States exhibit serologic evidence of previous *T. gondii* infection. Although the prevalence of prior infection increases with age, at no time does it attain the high incidence observed for a comparable population in certain tropical countries and France. Kapperud in a study from Norway found significant maternal risks factors to be, in order of decreasing probability, raw or undercooked minced meat products; undercooked mutton; eating raw or undercooked pork; cleaning the cat litter box; and washing the kitchen knives infrequently after preparation of raw meat, prior to handling another food item. In the United States, two to six women per thousand serosusceptible women will acquire the

infection during pregnancy. Approximately one-third of the females who acquire toxoplasmosis during pregnancy transmit the infection to their offspring. The later in gestation maternal infection is acquired, the greater the probability of fetal involvement.

When infection occurs during the first trimester of pregnancy, approximately 14% of the offspring will be infected; the figures for infection acquired during the second and third trimesters are 29% and 59%, respectively. The earlier the infection occurs in pregnancy, the more severe the disease is in the newborn. Almost all infected infants born to mothers who acquire the infection in the third trimester will appear normal at birth and only months or years later develop any clinical manifestations of the infection.



Postulated life cycle of *Toxoplasma* showing means of transmission by oocysts from cat feces and by ingestion of trophozoites or cysts from intermediate hosts. Days indicated represent time from ingestion of *Toxoplasma* by cat to the excretion of oocysts. Mice are shown to represent the many mammals and birds that can serve as facultative intermediary hosts and among which infection may spread, usually by carnivorism. Congenital transmission may take place during chronic infection as in mice, or during acute infection as in humans.

Figure 55.1 Postulated life cycle of *Toxoplasma gondii*

It is probable that the magnitude of the infective dose is an important determinant of whether an embryopathy ensues and what its pathogenic expression may be. A single oocyst contains eight sporozoites, in contrast to a single cyst, which may contain up to several thousand organisms. The impact of maternal infection with *T. gondii* in terms of fetal wastage and perinatal mortality appears to be directly related to the effects of the organism on the products of conception and is not due to the induced maternal reaction. The protozoa have been recovered or identified from aborted products of conception and

stillbirths. Maternal parasitemia during gestation may result in a wide spectrum of fetal involvement, ranging from seropositivity to full-blown congenital toxoplasmosis.

Infection with *T. gondii* in adults is not often symptomatic. Less than 10% of infection clinically manifests as disease. *Toxoplasma gondii* produces a spectrum of disease which includes toxoplasma lymphadenopathy, chorioretinitis, myocarditis, meningoencephalitis, and any whose clinical presentation resembles that of typhus. Overt disease is a poor indicator of the true prevalence of infection.

Within an obstetric population, the most commonly recognized manifestation of acute toxoplasmosis is lymphadenopathy. The lymphadenopathy may be the sole presenting sign or there may be an associated febrile response. The nodal enlargement may focally involve the cervical, supraclavicular or inguinal regions, and is frequently unilateral. The principal histologic characteristic of these lymph nodes is marked reticulum cell hyperplasia. This feature, in conjunction with the absence of significant lymphadenitis, accounts for the firm, non-tender, enlarged lymph nodes commonly observed. Any significant tenderness weakens the diagnosis of acute toxoplasmosis. The lymphadenopathy ordinarily is asymptomatic, but occasionally it may be associated with an infectious mononucleosis-like syndrome. With more advanced disease, fatigue is the most common presenting symptom in more severe infection.

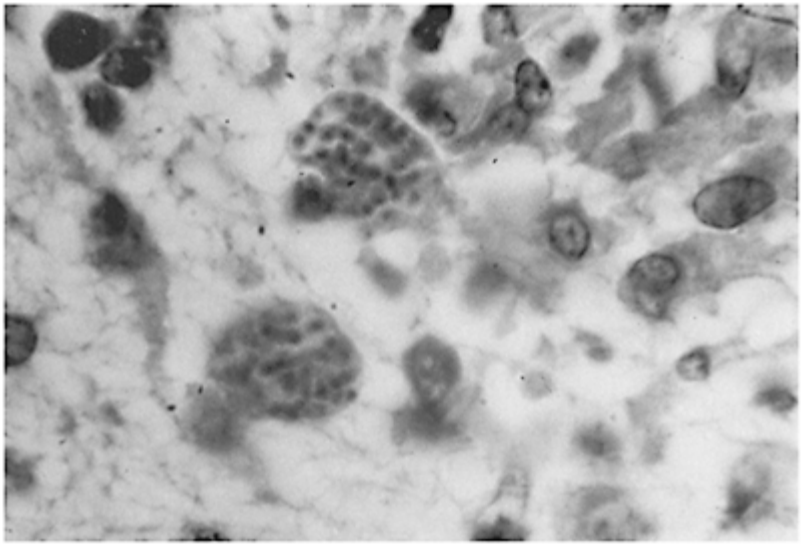


Figure 55.2 Encysted form of *Toxoplasma gondii* within glial cells (H&E, ×400)

It may be associated with headache, mental depression, myalgia, and a low-grade intermittent fever. A migratory polyarthritis and various types of predominantly macular rashes have also been described. In rare instances, abdominal pain secondary to mesenteric lymph node involvement may be the principal presenting complaint. In more

pronounced instances of systemic infestation, symptoms such as myalgia, myositis, and sustained fever are observed. Hepatosplenomegaly indicative of reticuloendothelial (RE) involvement can often be demonstrated. The severest manifestations of systemic disease are myocarditis, meningoencephalitis, or both.

The encysted forms begin to appear about the eighth day after infection (Figure 55.2). Viable residual cysts are demonstrable in muscle, intestinal mucosa, alveolar macrophages, brain, kidney, and uterus. Although they are regarded as dormant because of the absence of a host cellular response, it is postulated that such encysted forms may periodically be responsible for reactivation of infection. Although most cases of congenital toxoplasmosis are probably the result of hematogenous dissemination, the finding of toxoplasmal cysts in the uteri of normal females at hysterectomy, as well as postpartum in uterine curettage of gravidas who miscarried or aborted, suggested the possibility of an alternate route of transmission for congenital toxoplasmosis. Should implantation coincide with or impinge on a nidus of chronic infection, dissemination of the protozoon to the conceptus could occur by direct continuity.

CONGENITAL INFECTION

The incidence of congenital infection with *T. gondii* in the United States varies from 1 in 500 deliveries to 1 in 1300, depending upon geographic location. The first case of congenital toxoplasmosis was described in 1927. In the classic full-blown syndrome, the infant is usually premature or small for age, with microcephaly, intracranial calcification, abnormal cerebrospinal fluid (CSF) findings, and possible internal hydrocephaly (Figure 55.3), chorioretinitis, hepatosplenomegaly, jaundice, fever, and thrombocytopenia. The intracranial calcification, like that observed in first-trimester congenital cytomegalovirus infection, involves primarily the lateral ventricles (Figure 55.4).

At necropsy, multisystem involvement can be demonstrated, with chorioretinitis, perimyoendocarditis, meningoencephalitis, interstitial pneumonitis, nephritis, and focal adrenal necrosis. The trophozoite or its encysted form may be identified within virtually all of the major organ systems. Extramedullary hematopoiesis is usually marked.

The spectrum of neonatal involvement runs the gamut from the classic overt congenital toxoplasmosis to subclinical infection. The probability of congenital infection increases proportionally with respect to when in gestation maternal infection occurs. During the first, second and third trimester, approximately 15%, 30% and 60% respectively of the fetuses are estimated to become infected *in utero*.

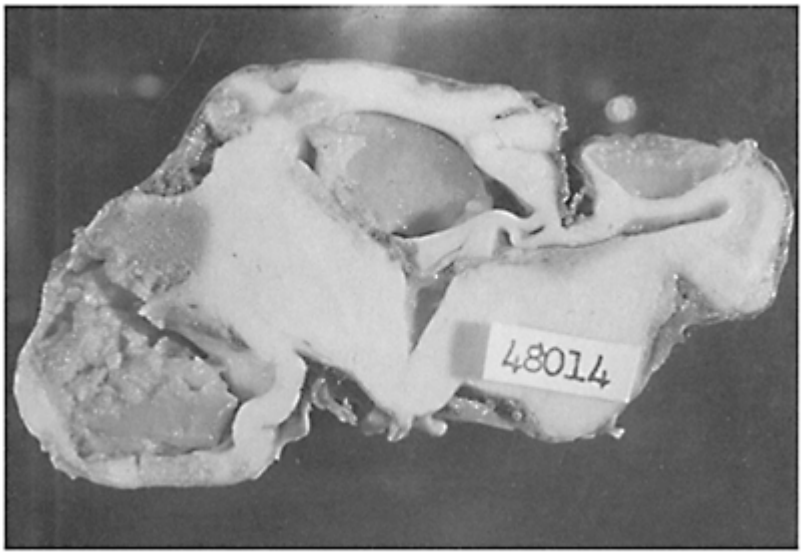


Figure 55.3 Marked distortion of the normal brain architecture (sagittal section) owing to massive tissue necrosis and secondary hydrocephaly (Courtesy of M.Kuschner, MD, Stoney Brook, NY)

There is a strong inverse correlation between time of infection acquisition and the severity of the ensuing infection in the fetus. The TORCH baby due to *T. gondii* is usually infected during the first trimester of pregnancy.

Second trimester fetal infection more probably results in *formes frustes* of the disease, that are more common than the full-blown syndrome. These clinical presentations are unexplained hepatomegaly or hepatosplenomegaly, disseminated intravascular coagulopathy present at birth, or jaundice in the first 24 hours of life. In these instances, the serum IgM level tends to be greater than 20 mg/ml. Elevation of the IgM level is a crude gauge of the chronicity of infection.

SUBCLINICAL CONGENITAL TOXOPLASMOSIS

Subclinical infection is documented by the demonstration of IgM antitoxoplasma antibodies in cord or neonatal serum, of encysted organisms within placental tissue, or of persistence of a significant antibody titer beyond six months of age. The incidence of asymptomatic congenital toxoplasmosis versus overt toxoplasmosis is approximately three or four to one. The significance

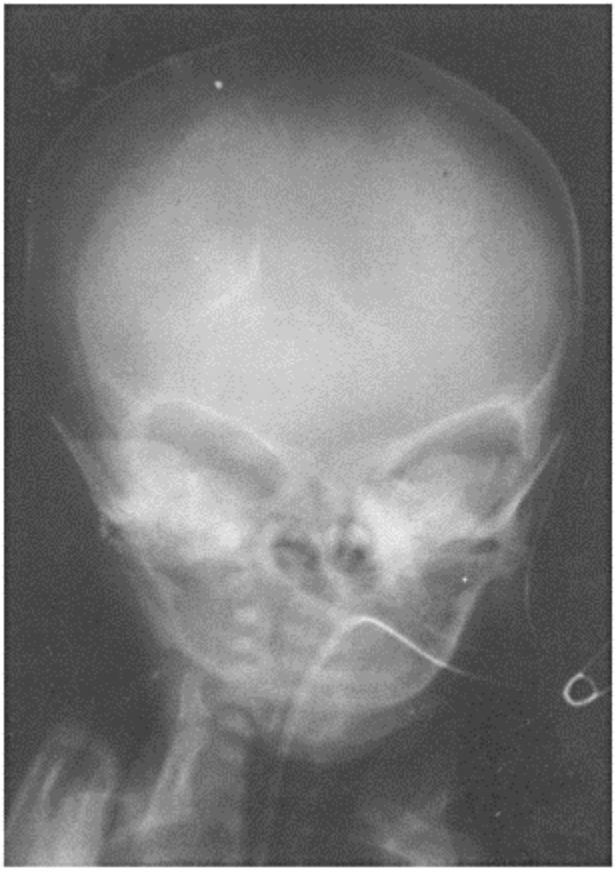


Figure 55.4 Skull X-ray demonstrating significant intracranial dystrophic calcification in the area of the lateral ventricles due to *Toxoplasma gondii*

of subclinical toxoplasmosis has been a matter of speculation. Glasser and Delta identified *T. gondii* in the chorionic villi, amnion, and umbilical cords of two monozygotic twins. The infants were normal at birth. At seven months both infants (under clinical observation) developed intracranial calcification, strabismus, and active chorioretinitis. As more information has become available, it is apparent that subclinical congenital toxoplasmosis has significant delayed morbidity (mental retardation or epilepsy in adulthood) and possibly mortality. In one study, by the age of 3½ years, 92% of such infants had untoward sequelae. Most cases of toxoplasmal chorioretinitis are probably due to congenital infection. That organ pathology, in most instances, is not complete at birth stresses the need for recognition of congenital infection in the immediate neonatal period and the institution of appropriate therapy.

CHRONIC OR RECURRENT MATERNAL PARASITEMIA

Although congenital transmission of *T. gondii* occurs in chronically infected animals, it has long been presumed that primary maternal infection with *T. gondii* had to occur during gestation in order to involve the conceptus. This concept is no longer held to be valid. Remington cultured 34 gravidas who exhibited serologic evidence of chronic toxoplasmosis and whose pregnancy terminated in abortion, stillbirth, or neonatal death. He recovered the organism in two cases of abortion and in one case of neonatal death.

Gravidas do not have to acquire primary infection during gestation to transmit the organism to the conceptus. While studying another infant with congenital disease, Remington isolated *T. gondii* from maternal blood at one, four and five months after birth. The mother was asymptomatic. Persistent parasitemia occurred despite high antitoxoplasma antibody levels.

Recurrent toxoplasmosis in severely immunocompromised individuals with CD4+ T-cell counts less than 50–100 cells/mm^3 is a well documented phenomenon.

Congenital infection in successive offspring may occur as a very rare event. Although the risk of a second infected infant appears infinitesimally small, it nonetheless exists. Langer recovered the organisms from the brains of two successive stillborn infants. Similarly, Garcia identified the organism in a conceptus, a live-born premature infant, and a six-month abortus, which comprised successive pregnancies in a given female. An additional well documented case has been recorded in Switzerland in which a congenitally infected infant was born to a woman who apparently acquired the infection approximately eight to 12 weeks prior to gestation. Following the birth of a congenitally infected infant, it may be prudent for the mother to use some form of contraceptive for at least one year. The question of whether or not to administer chemotherapeutic agents to the mother is

Table 55.1 Recommendations of the World Health Organization for acute toxoplasmosis in pregnancy

Up to the end of the 20th week of gestation, nine million units of spiramycin are orally administered daily for 4 weeks. After 4 weeks this regimen is repeated.
After 20 weeks of gestation, a 4 week course of sulfadiazine (1000 mg/day) in combination with pyrimethamine (25 mg/day) and solinic acid (10 mg/week) are administered. After a pause of 4 weeks this regimen is repeated. A maximum of three treatment cycles can occur between 20 weeks gestation and delivery.

very controversial. If therapy is instituted, it is for potential fetal and not for maternal considerations.

DIAGNOSIS

Maternal

Quantitative studies of the immunoglobulin (antibody) profile reveal that the initial response in acute acquired toxoplasmosis is the elaboration of IgM and IgA antibodies.

IgM specific antibodies appear early in the course of the disease. IgM can be detected by immunofluorescence antibody test (IFA), enzyme linked immunosorbent assay (ELISA), or the immunosorbent agglutination assay. The presence of antinuclear antibodies in sera may yield false-positive results. If available, the double-sandwich IgM-ELISA is a more sensitive and specific test than the IgM-IFA test or the standard IgM-ELISA test. Persistence of detectable IgM antibodies varies depending on the testing methodology. Most commercial kits for detection of IgM antibodies to *T. gondii* are not completely reliable according to the FDA Public Health Advisory of July 25, 1997. A report of a positive IgM titer should be confirmed using an accredited reference laboratory such as that of Dr. Jack Remington, Palo Alto Foundation Research Division (415–853–5014).

The positive predictive value of a positive IgM antibody test is lower than anticipated owing to its prolonged persistent acute infection. Gorgievski-Hrisoho *et al.* have contended that while the positive predictive value is lower, the negative predictive value (absence of IgM and IgA specific antibodies) is 100%. If one modifies the cutoff values for IgM and IgA immunoassays, the combination of the two tests improves the positive predictive value for recent infection results to 80%. In chronic toxoplasmosis the antibody is exclusively IgG; thus the possibility exists of distinguishing acute from chronic infection on the basis of the immunoglobulin profile.

Specific maternal IgG antibodies develop within seven to 10 days. These antibodies are long-lived and, consequently, in the absence of sequential specimens, may indicate only previous exposure to the organism.

The serologic diagnosis of recent infection with *T. gondii* can be inferred when specific IgG antibody titer has increased at least four-fold when two-fold dilutions of both acute and convalescent serum are tested simultaneously and/or IgM specific antibodies are demonstrable. A single high titer can be suggestive but not diagnostic of recent infection. High titers may persist for prolonged periods of time in selectedindividuals. A positive test for IgG antibodies and a negative test for IgM antibodies early in pregnancy indicate infection prior to gestation.

Fetal

The fetal response to the protozoon is sequentially comparable to that of the adult. However, the qualitative relationships are different. The fetus *in utero* responds to infection with *T. gondii* by elaborating IgM antibodies. This response may result in an overall elevation of the IgM level in the cord serum as well as the presence of specific IgM antibodies. This type of immunoglobulin predominates in the neonatal period and

during the first few months of life. Fetal infection early in gestation may not elicit a demonstrable IgM response.

The diagnosis of congenital toxoplasmosis in the neonate depends on either the demonstration of specific IgM or IgA antibodies or recovery of the protozoan. The persistence of specific antitoxoplasma antibody beyond the first six months of life usually reflects active infection. Whereas only approximately 25% of congenitally infected infants will be positive by the IgM-IFA test, 80% will be positive in the IgM-ELISA test. The demonstration of specific IgA in fetal or neonatal serum appears to be more sensitive than IgM for the diagnosis of congenital infection. Its diagnostic use to date has been limited by availability of testing facilities.

Infants first infected near to or at the time of delivery may have an IgM response only after several weeks. The presence of high levels of maternal IgG antibody in the fetus before exposure to the organism may suppress the ability of the infant to produce IgM antibody.

In the study reported by Grover *et al.*, detection of specific IgM antibodies correctly identified only three of the 10 positive fetuses. Because of these considerations, repeat testing of an infant's serum should be performed in any infant suspected on clinical grounds of having congenital infection but in whom initial testing does not show IgM specific antibody

A rapid diagnostic test using polymerase chain reaction (PCR) has been developed to detect the presence of specific antigen in lyzed, pelleted amniotic fluid cell samples. Grover *et al.* used this technique to correctly diagnose four cases of congenital infection *in utero*. In this study of 43 documented cases of acute maternal infection during gestation, there were no false-positive diagnoses. This technique will probably surplant the more time-consuming methodology, mouse inoculation with amniotic fluid and fetal blood. The antigens of the organism are detectable not only in amniotic fluid, cerebrospinal fluid and blood, but also urine.

Newer tests for the diagnosis of congenital toxoplasmosis are in development. Enzyme-linked immunofiltration assay and immunoblot have better sensitivities than the conventional IgM immunosorbent agglutination assay, IgM-ELISA, IgM-IFA test, *in vitro* culture and mouse inoculation.

T. gondii is an obligate intracellular parasite. All methods to cultivate it on synthetic media have been unsuccessful. However, it grows readily in a variety of tissue culture lines. The alternate isolation system for the recovery of the organism utilizes a biologic indicator system with the injection of infected material into the peritoneal cavity of seronegative mice. Isolation of tachyzoites from blood or other body fluids is proof of acute infection. Histological demonstration of tachyzoites in cytological preparations of body fluids or tissue sections is diagnostic of acute infection. Histological findings in lymph nodes obtained at biopsy are usually sufficient to document the infection.

In isolated instances, ultrasound studies may identify a fetus with advanced disease. The sonographic finding of significant ventriculomegaly usually correlated with significant neurological problems in life.

THERAPY

Therapy for maternal indications

Chemotherapy is indicated for individuals who have severe forms of toxoplasmosis or immunologic impairment of the host defense mechanisms.

The standard treatment in adults consists of pyrimethamine (Daraprim) (100 mg twice a day for the first day, followed by 50 mg a day thereafter) and sulfadiazene (1.5 g twice a day). The combination of pyrimethamine and sulfonamides is synergistic against trophozoites. The pyrimethamine-sulfadiazine-folinic acid regimen is alternated every three weeks with spiramycin (3 g daily) until delivery.

There is no effective therapy currently available against the encysted form of *T. gondii*.

Thrombocytopenia, agranulocytosis, or megaloblastic anemia may develop as a consequence of therapy. Baker's yeast 5–7 g daily or folinic acid 10–20 mg daily should be given concurrently to obviate hematologic toxicity. Women undergoing therapy should be closely followed with leukocyte assays, platelet counts, and hematocrit determinations bi-weekly. Pyrimethamine administration can result in megaloblastic anemia and/or pancytopenia.

Sulfadiazine can cause renal failure secondary to crystallization within renal tubules and severe epidermal necrolysis. Individuals receiving this drug need to drink ample fluids and avoid dehydration.

Because of concern of possible teratogenic consequences, the drug should not be administered in the first trimester in the absence of overriding maternal considerations.

Therapy for fetal indications

There is reservation about instituting therapy for an asymptomatic gravida with acute infection during gestation. The indications for therapy are those of potential fetal involvement and not of maternal derivation. Only 25–35% of women whose gestation is complicated by acute toxoplasmosis will give birth to a congenitally infected neonate. Preliminary data indicate that *in utero* chemotherapy with sulfadiazene and pyrimethamine and/or with spiramycin has the ability to alter the observed incidence of congenital toxoplasmal embryopathy (Table 55.1).

Wallon *et al.* reported on the effectiveness of therapy. They studied 490 infants whose mothers were treated during gestation. At one year of age, 77% of the infants were seronegative. Of the remaining 116 infants, 27% had cerebral calcification or ocular lesions. None had overt neurological impairment.

Therapy for maternal infection has shown that in fetuses who become infected despite maternal treatment, the clinical manifestations are greatly attenuated. With a normal antenatal sonogram and appropriate subsequent infant therapy the long-term neurological outlook for infected infants appears to be quite favorable.

An alternate approach to empiric therapy was that proposed by Daffos *et al.* which focuses on establishing documentation of fetal infection *in utero*. Once acute infection

documented by serological conversion and/or the presence of specific IgM anti-toxoplasma antibodies, at some time after 20 weeks of gestation, under ultrasonographic guidance, a minimal amount of blood was aspirated from the umbilical cord. At amniocentesis, 15 to 20 ml of amniotic fluid was obtained for intraperitoneal inoculation into seronegative mice. An additional parameter used to augment the probability of diagnosing *in utero* diseases was the finding of ventricular dilation on ultrasonography. In their prospective study of the documented cases of maternal toxoplasma infection, they were able to diagnose antenatally 39 of the 42 congenitally infected infants. Of the 15 fetuses who carried to term, all but two who had chorioretinitis remained clinically well. The organism was isolated from fetal blood in 64% of the 42 cases and from amniotic fluid in 52%. Specific fetal IgM was found in only 21 % of the cases. Unilateral or bilateral dilation of the ventricles occurred in 17 cases. In these cases, one pregnancy resulted in dizygotic twins. One died of congenital toxoplasmosis. The second infant had neither clinical nor serological evidence of disease.

In general, documented maternal infection is an indication for therapy irrespective of signs and symptoms of systemic disease. The therapeutic focus is aimed at attempting to avert or limit future organismal-cell interaction.

An informed consent should be obtained which clearly states that the gravida is aware not only of the potential problems associated with drug therapy but also that she will not benefit *per se* from therapy. There should be a willingness on the part of the mother to share the responsibility of drug therapy. For first trimester maternal infection, it is recommended that therapy be withheld during the period of organogenesis. Only one-third of the fetuses will actually require therapy, yet 100% of the fetuses will be subject to drug exposure during the critical periods of organogenesis.

The Europeans advocate the use of spiramycin as soon as the diagnosis of maternal infection is established. Once organogenesis is completed, a combination treatment regimen using pyrimethamine, sulfadiazine, and spiramycin is implemented, because spiramycin does not reliably cross the placenta.

Pyrimethamine should not be used in the first 16 weeks of pregnancy because of concern for teratogenicity (in this circumstance sulfadiazine should be administered alone).

Sulfonamides should be discontinued two to three weeks prior to the expected date of confinement to avert the problem of competitive antagonism with bilirubin in the postpartum period. The sulfonamides successfully compete with bilirubin for the albumin binding site. Extensive displacement of bilirubin from albumin binding sites can be responsible for the induction of kernicterus in the neonate.

Comparative tests have shown that sulfapyrazine, sulfamethazine and sulfamerazine are about as effective as sulfadiazine. Sulfathiazole, sulfapyridine, sulfadimetine, and sulfisoxazole are much less effective and are not recommended. The usual dosage of sulfadiazine or triple sulfonamides is 50 to 100 mg per kg of body weight every 24 hours in two to four equal doses by mouth.

Pyrimethamine is a folic acid antagonist that will cause a reversible and gradual depression of the bone marrow. Although toxicity is dose-related, absorption of the drug is not uniform in all patients. Platelet depression, with its associated bleeding tendency, is the most serious consequence of toxicity. Both leukopenia and anemia may occur as well. Other side effects are gastrointestinal distress, headaches and a bad taste in the mouth. All

patients treated with pyrimethamine should have a peripheral blood cell and platelet count ideally twice a week. Folinic acid (in the form of leucovorin calcium) has been used to lessen the effects of the drug on platelets (5–15 mg per day intramuscularly). Five grams of baker's yeast daily has been used in lieu of leucovorum.

MANAGEMENT IN PREGNANCY

Routine serological screening for toxoplasmosis is probably not cost effective; however, limited screening of gravidas who like raw or poorly cooked meat, who have significant contact with animals or who do extensive gardening is advocated. IgG specific antibodies will be present in a significant number of these patients. Only those gravidas with a concomitant specific IgM titer need further evaluation and management.

All gravidas who are immunologically compromised or immunosuppressed should be screened for the presence of anti-toxoplasma antibodies. Seropositive women need to be carefully monitored for potential reactivation of disease.

PREVENTION

Toxoplasma infection of the pregnant female is preventable. This is accomplished by avoidance of the ingestion of cysts or sporulated oocysts by the seronegative woman. Cysts are rendered non-infective by heating meat to 66ºC or by smoking or curing it. Freezing is less reliable since it requires temperatures (−20°C) not achieved by most home freezers. Raw fruits and vegetables should be thoroughly washed and specific steps taken to prevent access of flies, cockroaches and other insects to animal feces. Hands should be washed thoroughly after handling raw meat or vegetables. The handling of cat feces should be avoided altogether. If this is not possible, disposable gloves should be worn when disposing of cat litter and when gardening out of doors. Treatment of the cat litter pan with nearly boiling water for five minutes will kill potentially infective oocysts.

In a recent study of risk factors, frequent contact with soil may be more important a risk for maternal infection than the household presence of a cat. The key elements in preventing maternal toxoplasmosis include cooking meat until it is well done, washing fruits and vegetables and wearing gloves when working in the garden (if cats frequent the area) or disposing of cat litter.

There are no drugs to kill *T. gondii* tissue cysts in human or animal tissues. Freezing to −20°C, cooking to an internal temperature of 66ºC, orgamma irradiation (0.5 kGy) can kill tissue cysts in meat.

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Trichomonas vaginalis

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Observing animals on slides of purulent discharges from the genital tracts of men and women, Donne in 1830 termed the organisms Trichomonas vaginale. The name *Trichomonas vaginalis* was suggested two years later by Ehrenberg. Since then, over 100 separate species of the genus *Trichomonas* have been reported, but only three have been isolated in humans. *Trichomonas vaginalis* is the only species of the trichomonads that is pathogenic for humans. *T. tenax* and *T. hominis* infect the human gastrointestinal tract, but as harmless commensals.

While primarily a sexually transmitted disease (STD), the demography of disease suggests that it may be transmitted by an alternate mode. Prevalence studies have demonstrated two peaks: one in young sexually active women and a second peak in older women who have no evidence for sexually transmitted infection.

T. vaginalis is a tetraflagellated, motile protozoon with an anterior nucleus, an anterolateral undulating membrane, and a prominent axostyle (Figure 56.1). Usually the organism's shape is oval or fusiform and its size is slightly larger than that of the average leukocyte (15Ê). However, under adverse conditions or with certain strains, its shape may be round or pear-shaped, and its size considerably smaller (7Ê-13Ê) or larger (20Ê-30Ê) (Figure 56.2). An oval nucleus, which appears more dense than the surrounding cytoplasm, is located toward the flagellated pole and is usually 1/3–1/2 the length of the organism. The cytoplasm is basically clear but frequently contains varying amounts of cytoplasmic particles, vacuoles, debris, and bacteria. Rarely, intracytoplasmic leukocytes or erythrocytes may be identified. Reproduction is by mitotic division of the nucleus and longitudinal fission into two daughter cells. The organism is believed to exist only in the trophozoite form; a cyst form has not been found.

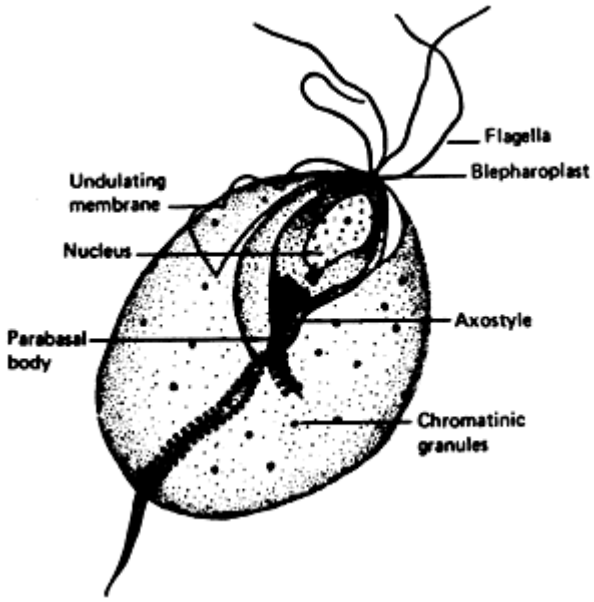

Figure 56.1 Diagram of *Trichomonas vaginalis*

The viability and growth of *T. vaginalis* are supported when its milieu is moist, the pH is 4.9–7.5, and the temperature is 35°–37°C. The more robust and usually smaller organisms are observed in the pH range of 5.5–5.8 and the less motile and often larger organisms are encountered when the pH is higher or lower than optimum. It is believed that *T. vaginalis* is a facultative anaerobe because it forms lactic acid and carbon dioxide from sugars and starches, but excessive oxygen reduces carbohydrate metabolism and depresses growth. Culture media should contain cysteine, peptone, proteolysed liver, maltose, serum, and antibiotics. Estrogen has no effect on growth in culture.

The organism is killed on drying or after prolonged exposure to sunlight and it will not survive more than

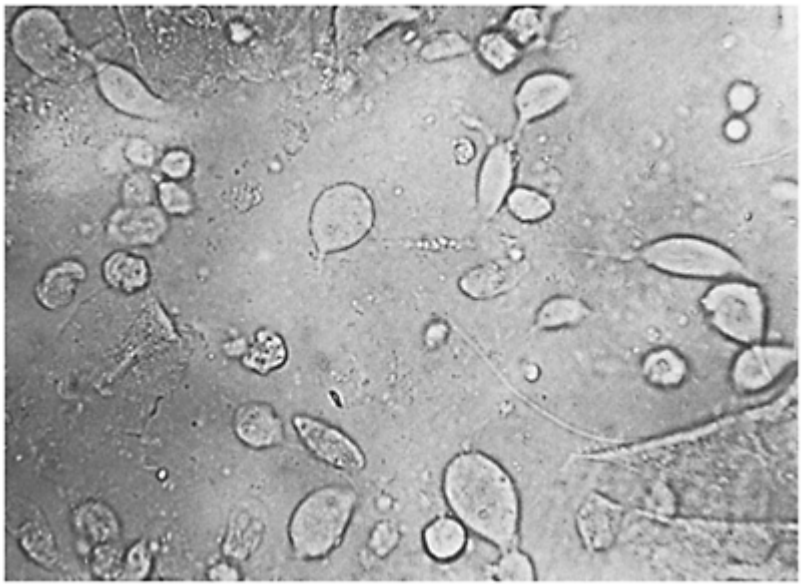

Figure 56.2 Variation in the size and configuration of *Trichomonas vaginalis*

5 days at 0°C, 30 minutes in tap water, 4 minutes at 50°C, or 6 hours in warm saline.

NATURAL HISTORY OF THE DISEASE

Man is the only known host of *T. vaginalis*. In women the organism usually infests the vagina and urethra but may involve the endocervix, Bartholin's glands, Skene's glands, or the bladder. Isolated cases have been reported in which the protozoon was recovered from the uterus, fallopian tubes, and renal pelvis. In men the organism usually colonizes the lower urethra, but occasionally it infests the prostate gland, seminal vesicles, or epididymis.

Prevalence

The prevalence of *T. vaginalis* is unknown, but it is worldwide in distribution and has been demonstrated in each society and subculture in which it has been sought. As a global estimate, approximately 15–20% of all women and 3–10% of all men harbor the organism.

Sources of Infection

Trichomonas vaginalis is ordinarily transmitted through sexual intercourse, with the female being the primary reservoir and the male the vector. When chronically infected, the male may also act as a reservoir. Once the female is infected, spontaneous eradication of the disease is extremely rare and, if it is untreated, the organism appears to survive indefinitely in the lower urogenital tract. In recent studies of male consorts of infected females, the organism was cultured from the lower urethra in over 90% of the cases. However, in the male, spontaneous decolonization of the lower urinary tract occurs within three weeks unless reinoculation intervenes or there is chronic trichomonad infestation of the prostate, seminal vesicles, or epididymis.

While primarily a STD, the demography of disease suggests that it may be transmitted by an alternate mode. Prevalence studies have demonstrated two peaks: one in young sexually active women and a second peak in older women who have no evidence for sexually transmitted infection.

Neonates and infants may develop trichomonad infection in the vagina and lower urinary tract when delivered vaginally of an infected mother. Since the vagina of a young girl is not optimally suited for growth of the organism, inoculation at birth has been postulated as leading to a latent, low-grade colonization during prepubescence. With the onset of puberty, optimal growth conditions for the trichomonad develop in the vagina, and thereafter the disease begins its clinical manifestations.

Numerous studies suggest the possible transmission of *T. vaginalis* by public toilets, saunas, swimming pools, washcloths, bath towels, and unsterile pelvic examination techniques. Under the appropriate conditions, each of the foregoing may transmit infection but in reality its occurrence is probably rare.

The mechanism whereby *T. vaginalis* evokes clinical infection remains an enigma. Under experimental conditions, induction of clinical disease in a healthy human vagina requires inoculation of large numbers of organisms and an incubation period of several weeks, but intravaginal inoculation of one viable trichomonad may, under ideal growth conditions, induce colonization.

Several physiologic and pathologic states of the vagina or of the host appear to enhance the viability and growth of *T. vaginalis* and perhaps activate its pathogenicity. These environmental conditions are interrelated and often additive in their effects on the protozoon's growth. However, in individual cases of trichomoniasis, it is not uncommon to encounter a single, predisposing growth factor which predominates over other factors known to inhibit *T. vaginalis*.

Mature vaginal epithelium

Owing to stimulation by circulating estrogen, the mucosa of the healthy adult vagina consists of mature, glycogenated squamous epithelium, and the vaginal cavity contains free, glycogen-derived glucose, which is essential for growth of *T. vaginalis*. Clinically symptomatic trichomoniasis occurs most frequently during the reproductive years when ovarian output of estrogen is maximal, the epithelium of the vagina is most mature, and the vagina contains large amounts of glucose. Prepubescent girls and estrogen-deficient

women (castrates or postmenopausal) harboring the trichomonad are usually asymptomatic. Exacerbation of trichomoniasis is not uncommon soon after starting estrogen replacement therapy in an estrogen-deficient menopausal patient.

Elevated vaginal pH

The healthy adult vagina contains large numbers of *Lactobacillus acidophilus* which metabolize the free glucose into lactic acid, thereby maintaining the vaginal pH at 3.5–4.5 and creating an unfavorable environmental pH for the growth of most vaginal pathogens, including *T. vaginalis* (optimal pH 5.5–5.8).

Certain conditions, however, may temporarily elevate the vaginal pH and encourage the growth and colonization of *T. vaginalis*. These include:

(1) progesterone-dominant states such as pregnancy;
(2) the presence of intravaginal secretions such as menstrual blood, excessive cervical mucus, or exudate from cervical or vaginal lesions; and
(3) the more alkaline vaginal milieu engendered by pathologic alterations of the vaginal flora such as certain bacterial overgrowths (*Staphylococcus aureus*, alpha-streptococcus), with a consequent reduction in lactobacilli.

Hesseltine *et al.* demonstrated that induction of clinical trichomoniasis in human volunteers was facilitated when large numbers of other bacteria and a few lactobacilli populated the vagina.

As significant colonization and multiplication of *T. vaginalis* ensues, a corresponding and directly related rise in vaginal pH may occur—initially due solely to the trichomonad population. This encourages bacterial overgrowth, inhibits lactobacillus production, and establishes the infestation of the organism. Specific eradication of the trichomonad with metronidazole promptly returns the pathologic process (the reduced lactobacilli, the altered bacterial flora, and the elevated vaginal pH) to normal.

Pre-existing vaginal or cervical lesions

Any vaginal or cervical lesion capable of weakening or destroying the surface epithelium may allow access of *T. vaginalis* to either the deeper epithelium or the submucosa, there by creating more intense inflammation, discharge, and other symptoms. Some of these lesions include trauma (from tampons or chemicals), certain bacterial infections, cervicitis, candidiasis, genital herpes, and certain neoplastic lesions (carcinoma and condyloma acuminatum).

HISTOPATHOLOGY

The histologic findings of acute *T. vaginalis* infection are non-specific and similar to other superficial, inflammatory reactions of the vagina and urethra. There is diffuse or patchy blood vessel dilation and proliferation in the surface epithelium and submucosa. Tufts of capillaries (double-crested) may be observed to permeate the epithelium.

This vascular engorgement, combined with a variable degree of polymorphonuclear leukocyte infiltration and elongation of the papillae, may resemble an acute papillitis. In severe infections the outer portions of the surface epithelium may become detached and replaced with an inflammatory exudate. In chronic trichomoniasis the inflammation is less severe, with lymphocyte and plasma cell infiltration, but the surface epithelial cells often show intracellular edema, vacuolization, and a perinuclear halo or 'chicken wire' effect. The nuclei of these cells may be enlarged, hyperchromatic, and irregular. However, the outward maturation of the epithelial cells progresses normally. True tissue invasion or involvement of endocervical glands by the trichomonad is extremely rare.

Cytopathology

Although *T. vaginalis* may be identified in only 15% (range 7–30%) of Papanicolaou smears in large, unselected, cervical cancer screening programs, approximately 30–40% of all abnormal cytologic smears are associated with the identification of *T. vaginalis*. In patients with urogenital trichomoniasis, 2–8% will have an abnormal cytologic smear which is usually interpreted as an atypical smear (class II), but not infrequently a suspicious smear (class III) or even a rare class IV (usually overinterpreted) may be attributed to cytologic alteration by *T. vaginalis*.

Characteristically, the smear is 'dirty' with large numbers of leukocytes, necrotic cells, clumped bacteria, cellular debris, and occasionally *Leptothrix* in the background. Clusters of leukocytes overlying squamous cells are common but non-specific. The trichomonad appears as a gray-green, round or fusiform 'blob' with an eccentrically located, slightly denser nucleus. The flagella are not usually seen.

Of clinical importance is the curiosity that, in premenopausal woman, trichomoniasis tends to increase the number of intermediate and parabasal cell types, thereby yielding a falsely low estrogen activity, whereas in postmenopausal patients the organism tends to induce the growth of the more mature intermediate and superficial cells, yielding a falsely high level of estrogen activity. These trichomonad-induced alterations of the epithelial cells make the estimation of estrogen activity on cytologic smear in patients with trichomoniasis of dubious value.

An abnormal cytologic smear due to *T. vaginalis* infestation will revert to normal within 6 to 12 weeks after eradication of the organism with metronidazole therapy, but even if a previously abnormal cytologic smear returns to normal, these patients should have repeat smears performed every four months for at least one year. If the cytologic abnormality persists after metronidazole, and there is no evidence of recurrent or persistent trichomonad infestation, appropriate colposcopy-directed biopsies of the cervix and endocervix should be obtained for histologic diagnosis of the cytologic changes.

CLINICAL PATTERNS OF TRICHOMONIASIS

In women, urogenital trichomoniasis is one of the major causes of vulvovaginitis and abnormal cervicovaginal cytology. In men, *T. vaginalis* produces a mild, transient, and usually asymptomatic urethritis. Trichomonad infestations of the prostate gland, seminal vesicles, and epididymis occur but are uncommon.

The symptomatology of vulvovaginitis is non-specific and consists of variable degrees of vaginal discharge, perineal odor, itching, burning, vulvar swelling, introital tenderness, dyspareunia, dysuria, and urinary frequency. Trichomoniasis alone accounts for about 15% to 20% of vulvovaginitis but in another 10% to 20% of cases, the trichomonad coexists with one or more additional vaginal pathogens. *T. vaginalis* frequently co-exists with bacterial vaginosis to such a degree that symptomology characteristic to the latter is often attributed to trichomoniasis.

The clinical patterns of urogenital trichomoniasis in women consist of:

(1) asymptomatic trichomoniasis;
(2) symptomatic trichomoniasis, acute and chronic forms;
(3) recurrent or persistent trichomoniasis after metronidazole therapy; and
(4) neonatal and prepubescent trichomoniasis.

Asymptomatic

Approximately 70% of women harboring *T. vaginalis* are asymptomatic carriers of the organism. In a study of inner-city gravidas who presented for prenatal care, 9.4% were infected with *T. vaginalis*. Only 18.2% of infected women had vaginitis-related symptoms prior to the pelvic examinations.

Characteristically, the patient fails to experience any symptom usually associated with the disease. The pelvic examination shows no objective signs of tissue reaction, the vaginal pH is normal, and lactobacilli are present. It is postulated that in these women, either the vaginal environment is temporarily unfavorable for progressive growth of *T. vaginalis* or the particular organism is a less virulent strain incapable of evoking significant tissue response and symptoms.

Since all women with asymptomatic trichomoniasis are capable of transmitting the disease, and many will eventually become symptomatic, therapy is indicated.

Symptomatic—acute form

The symptoms of acute urogenital trichomoniasis are variable. The patient may exhibit profuse, frothy, gray, and malodorous vaginal discharge associated with severe itching, redness, swelling, and tenderness of the introitus; and complain of dyspareunia, dysuria, and urinary frequency (Figures 56.3 & 56.4). Uterine tenderness may be present. But this classic syndrome accounts for only 10% of cases. Usually the symptoms are less severe.

Patients with the acute form may have copious watery vaginal discharge requiring a perineal pad for control. Others, with scanty discharge, may complain of severe introital tenderness, swelling, dyspareunia, or dysuria. An occasional patient may have postcoital spotting, menorrhagia, or dysmenorrhea due to increased pelvic vascularity wrought by extensive trichomoniasis. Rarely, inguinal adenopathy is observed. Pregnancy may exacerbate the symptoms.

The examination usually discloses moderate erythema, edema, and tenderness of the introitus and lower side walls of the vagina. The erythema and edema of the upper vagina and ectocervix are usually diffuse. There is often a mild cervicitis. Small areas of subepithelial hyperemia of the vaginal mucosa and cervix can be demonstrated with colposcopy. When grossly discernable, punctate submucosal hemorrhages are often

referred to as the ‘strawberry’ cervix or vagina. Frequently, the vaginal fornices contain slightly raised, coarsely nodular, and often indurated patches of submucosal edema and inflammation. The character of the discharge is non-specific. It may be thin, thick, or mucoid, and its color may be white, gray, yellow, or green. It usually has a disagreeable odor and sometimes contains small bubbles, but these findings may be associated with other vaginal infections, such as vaginal bacteriosis. Characteristically, lactobacilli are absent, and the vaginal pH is above 5.5.

Wet mount examination reveals, in addition to the presence of trichomonads, a significant number of white blood cells and a disruption of the vaginal bacterial flora. Between 30% and 60% of women with acute symptomatic disease have a positive volatile amine test and demonstrate the presence of clue cells.

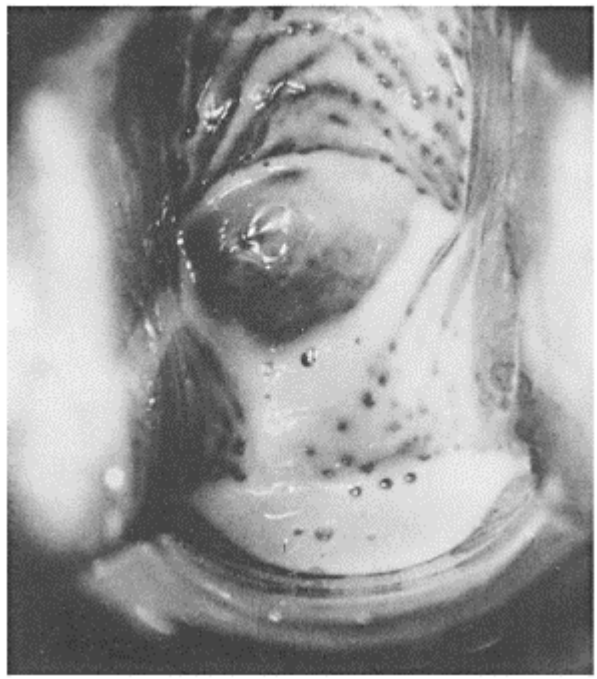

Figure 56.3 Trichomoniasis with a ‘strawberry vagina’ is above. While diagnostic when present, this finding is seen in only a few of the patients with the infection

Symptomatic—chronic form

The most frequent type of symptomatic trichomoniasis is the chronic form. Usually women with the chronic form of the infection have a long history of intermittent

vulvovaginitis, with many having been treated repeatedly with various topical preparations. Some patients choose to endure the symptoms, whereas others temporarily alleviate them by self-medication with douches, perfumes, and other proprietary preparations.

The complaints vary but are usually mild. There may be slight to moderate, malodorous vaginal discharge, perineal itching, or dyspareunia.

Pelvic examination usually reveals mild introital erythema and tenderness, and white, gray, or slightly yellow mucoid discharge which may be malodorous and contain a few bubbles. The mucosa of the vagina and cervix usually shows no gross evidence of significant inflammation, but despite this, abnormal Papanicolaou smears are relatively frequent in patients with chronic

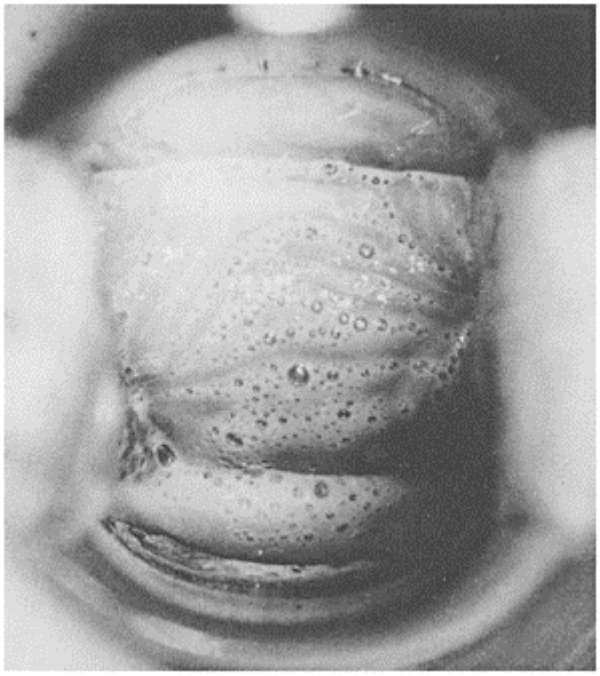

Figure 56.4 Marked frothiness, when present, is usually a sign of trichomoniasis but frothiness is usually minimal and present in only about 10% of the patients with trichomonal infections

trichomoniasis. Lactobacilli are reduced in number, and the vaginal pH is usually over 4.5.

NEONATAL AND PREPUBESCENT TRICHOMONIASIS

The neonatal infant or the prepubescent female may asymptomatically harbor *T. vaginalis* or may develop symptomatic vaginal discharge, itching, sleeplessness, or pyuria. Most cases in the newborn infant are transmitted during vaginal delivery in a trichomonad-infected mother.

Symptomatic trichomoniasis in young girls is encountered most frequently in the first few months of life and 1–2 years prior to menarche. A somewhat higher level of circulatory estrogen and a relatively more mature vaginal epithelium, which occur during these periods, appear to augment the growth and the subsequent symptomatology of the trichomonad.

Symptomatic trichomoniasis is less common in the 1 to 9 year age group, when maternally derived estrogen is no longer present and when the ovarian output of estrogen is minimal. However, a latent or asymptomatic phase of *T. vaginalis* infestation may exist during these early years.

TRICHOMONIASIS IN PREGNANCY

Several studies have suggested that pregnant women infected with *T. vaginalis* may be at increased risk of an adverse perinatal outcome. In a multi university-affiliated hospital study of 13816 patients, Cotch *et al.* found that pregnant women infected with *T. vaginalis* at mid-gestation were statistically significantly more likely to have a low birthweight infant and to deliver preterm. Compared with whites and hispanics, *T. vaginalis* infection accounts for a disproportionately larger share of the low birthweight rate in blacks. In contrast, a smaller study by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network of 2 929 gravidas at 10 centers failed to detect a significant association between infection with *T. vaginalis* and preterm births.

Neither study subdivided gravidas with trichomoniasis into acute versus chronic and with or without concomitant vaginal bacteriosis. Meis *et al.* and McGreagor *et al.* have demonstrated that the presence of vaginal bacteriosis at 22 and 28 weeks gestation was statistically associated with an increased risk of spontaneous preterm births. McGregor *et al.* have similarly demonstrated that orally-administered clindamycin treatment was associated with a 50% reduction of bacterial vaginosis linked preterm birth and preterm premature rupture of membranes. There is a growing movement to screen all gravidas at risk for preterm births for bacterial vaginosis or common genital tract infections.

Of added interest, The Vaginal Infections and Prematurity Study Group, who evaluated the relationship of frequent sexual intercourse, preterm delivery and vaginal colonization with specific microorganisms, found that frequent sexual intercourse by itself is not associated with an increased risk of preterm birth. However, women who are colonized with *T. vaginalis* and *Mycoplasma hominis* and who engage in frequent intercourse are at increased risk for preterm delivery.

DIAGNOSIS

The diagnosis of all types of vulvovaginitis, including urogenital trichomoniasis, is considerably more accurate and conclusive if the patient has been instructed not to douche or use any form of topical vaginal preparation (contraceptives or antivaginitis creams, foams, or suppositories) for 48 hours prior to examination.

After a careful history, the external genitalia are examined. The urethra, periurethral glands, and Bartholin's glands are milked, and the vagina and cervix are visualized with a dry unlubricated sterile speculum. Appropriate cultures, a wet smear, a cytologic cancer smear, and often certain biopsies are necessary to determine the presence or absence of other common vaginal and cervical diseases that may cause vulvovaginitis or that may coexist with urogenital trichomoniasis, such as candidiasis, *Gardnerella vaginalis* infection, gonorrhea, genital herpes, chronic cervicitis, condyloma acuminatum, or cervical carcinoma.

Urogenital trichomoniasis cannot be diagnosed with any reasonable degree of accuracy on the basis of the history and the objective signs found on pelvic examination. The only acceptable methods of diagnosis are wet smear and/or cultural identification of the viable trichomonad.

Wet smear

The wet smear identification of *T. vaginalis* is rapid and inexpensive and, in symptomatic patients, at least 80–90% reliable. A fresh specimen of vaginal discharge or urine sediment is mixed with a drop of warm saline on a slide, topped with a coverslip, and examined quickly with a microscope (light phase, or darkfield). Under low power the organism usually moves actively in a jerky and twisting fashion due to the lashing and waving motions of the anterior flagella and the undulating membrane. If no obvious activity is apparent, higher-power observation and some experience are necessary to identify the action of the undulating membrane or the inconspicuous ameboid movement of sluggish organisms.

Culture

The inoculation of a suitable transport medium (Stuart or thioglycollate) with the subsequent culture, incubation, and microscopic identification of viable *T. vaginalis* is expensive and time-consuming. It is the most sensitive and accurate means of detecting *T. vaginalis* in cases of suspected male trichomoniasis, in cases of refractory, undiagnosed vulvovaginitis, and in most investigational studies of the protozoon. The commercially available Feinberg-Whittington or Kupferberg (simplified trypticase serum) culture media are both satisfactory for clinical practice, but Diamond's or Lowe's media are more sensitive.

Cytological smears

The Papanicolaou cancer smear is not a reliable method for the detection of *T. vaginalis* since most cytopathology laboratories report considerable errors, both false-positives and false-negatives, in the identification of the organisms. Therefore, confirmatory identification of viable organisms by the wet smear or culture techniques is essential before treatment of any patient with 'trichomonads' initially identified on cytological smear.

The Gram or Giemsa staining methods of *T. vaginalis* are somewhat more time-consuming and probably of no greater accuracy than the wet smear preparation.

Although identification of the trichomonad is the basic starting point in the diagnosis and the subsequent therapy of urogenital trichomoniasis, the true etiology of the patient's symptoms and pelvic findings must always be regarded as uncertain until all signs and symptoms, including an abnormal Papanicolaou smear, have been completely resolved after specific management.

THERAPY

Eradication of organisms from the genital or urinary system depends upon the administration of a systemic agent.

Metronidazole is the only effective agent approved for treatment of trichomoniasis in the United States. No vaginal medication will eradicate organisms from Skene's duct and urinary tract. Instillation of topical trichomonacidal drugs into the urethra and bladder of either sex is ineffective. Metronidazole is the only effective agent available which eradicates trichomonads from the host.

The remarkable success of oral metronidazole is due to its antitrichomonal activity in the urine, serum, glands, and other tissues enabling it to treat those trichomonadinfested anatomical areas of the genitourinary tract (urethra, bladder, periurethral glands, Bartholin's glands, endocervix, prostate, and seminal vesicles) inaccessible to topical preparations. Metronidazole in a single 2 g dose produces peak serum levels of 40 g/ml. Its serum half-life is approximately eight hours. Levels of metronidazole in breast milk equal the serum concentration. Approximately 20% of an ingested dose is excreted unchanged in the urine.

Metronidazole requires the reduction of its nitro group to oxidize organismal DNA which results in cell death. *In vitro,* trichomonads are rendered non-viable when in contact with metronidazole for approximately 4 hours.

The dosage schedules of metronidazole most widely employed are:

250 mg three times a day for 5–7 days

500 mg three times a day for 3 days

500 mg every 12 hours for 5–7 days

2 g single stat bolus

If the patient can swallow the larger pills, four 500 mg pills are more economical than eight 250 mg pills. Bolus administration and 5–7 day regimens are equally effective in the treatment of uncomplicated trichomoniasis. Higher cure rates are achieved when the male consort is concomitantly treated. Post-therapy vulvovaginal candidiasis (Ping-Pong vaginitis) is more common in association with the multi-day therapy.

The clinical response to treatment with metronidazole is often dramatic. Symptoms abate in a few days and local tissue alterations usually resolve in 3–6 weeks.

Table 56.1 Treatment of metronidazole-resistant trichomoniasis

Resistance to metronidazole is relative, not an all-or-none phenomenon
Mild to moderate resistance
Most cases can be cured by increased dosages of metronidazole. As a rule of thumb, doubling the initial recommended dose and extending the duration of therapy by two days is usually all that is required
Moderate to severe resistance
Select to treat patient in mid-cycle. Have patient use saline douches twice a day for at least three days prior to therapy. Mechanically cleanse the vagina with initially H_2O_2 and then paint with gentian violet.Then administer metronidazole 2.5–3 g daily for 14 days, part of this dose given as metronidazole suppositories. Patients must be **very** closely monitored for adverse drug reaction

Metronidazole-induced complications are usually mild and occur in less than 10% of cases. Most are orally or gastrointestinally related, such as dry mouth, metallic or bitter taste, glossitis, stomatitis, furry tongue, anorexia, nausea, epigastric or abdominal pain, vomiting, or diarrhea. Central nervous system (CNS) reactions are rare, but headache, dizziness, vertigo, ataxia, confusion and depression have been reported. A few patients have developed a drug-related rash or urticaria, and a dark urine has been ascribed to a metabolite of metronidazole. A transient, mild and reversible neutropenia has been reported and patients receiving frequent courses of metronidazole therapy should have blood count monitoring before, during and after therapy. Because of a disulfiram-like effect, ingestion of alcohol during or immediately following metronidazole therapy may induce an annoying clinical syndrome comprising many of the gastrointestinal and CNS symptoms.

Fetal considerations

Animal studies have demonstrated the ability of metronidazole to function as a mutogen. To date, no recognizable teratogenic or adverse neonatal effect has been demonstrated. Nevertheless, drug administration during the first 16 weeks is best delayed for theoretical reasons.

Sexual partner therapy

To prevent reinfection, treatment of a patient's sexual consorts is imperative. Therapy of the male partner may reduce transmission of infection to other females. Males refusing therapy should use a condom for four weeks after initial treatment of the female.

METRONIDAZOLE-RESISTANT *TRICHOMONAS VAGINALIS*

Induction of resistance of *T. vaginalis* to metronidazole can be demonstrated both *in vitro* and *in vivo*. With serial passage *in vitro* of an initially moderately resistant strain to increasing concentrations of metronidazole, the minimal inhibitory concentration (MIC) of metronidazole will increase from less than 0.2 μg/ml to greater than 50 μg/ml. With repeated passage of the organism in mice treated with suboptimal doses of metronidazole, the activity of metronidazole will be 14 to 48 times less than that of the original strain.

There are no well-established protocols for the therapy of metronidazole-resistant *T. vaginalis*. The majority of cases have relative, rather than absolute resistance.

Most patients who fail to respond to bolus or 500 mg bid×5–7 days represent a composite of individuals with either poor compliance, reinfection, or relative resistance.

Management of a patient with persistent trichomonas following metronidazole therapy involves initially doubling the prescribed therapeutic dose, prolonging the duration of administration, and having the patient refrain from sexual activities and/or douching (Table 56.1). Tinidazole (not available in the United States) has a longer half life than metronidazole. Use in the therapy of resistant trichomoniasis involves the standard dose administered over twice the established duration.

Failure to respond to increased dosing and prolonged duration of therapy warrants obtaining metronidazole susceptibility testing. A prewarmed culture tube should be inoculated and mailed by overnight delivery service to a reference laboratory capable of performing susceptibility testing. The patient may be placed on intravaginal clotrimazole in an attempt to ameliorate her symptoms while awaiting the results of the *T. vaginalis* susceptibility testing.

Therapy of metronidazole-resistant *T. vaginalis* involves aggressive use of metronidazole. Concomitantly, one gram of metronidazole in an appropriate vehicle can be administered intravaginally at bedtime. Five grams of metronidazole gel (37.5 mg of metronidazole) may be used intravaginally bid as an adjunct to high-dose oral therapy in highly resistant cases. Dosages of metronidazole required for cure are not approved by the FDA and may be associated with a high incidence of adverse drug reactions. Administration of 4–6 g or more daily has been associated with seizures and a potentially disabling peripheral neuropathy.

How long parenteral therapy should persist is speculative. Many clinicians will do daily wet mounts. As soon as the wet mount becomes negative, the dosage is reduced and therapy is continued for two to four additional days.

PROPHYLAXIS FOR VULVOVAGINAL TRICHOMONIASIS

Postcoital douching with an acid preparation soon after intercourse, contraceptive creams, jellies and foams with trichomonadal properties (if used before and after intercourse), condoms, and prophylactic use of metronidazole have all been advocated for the prevention of reinfection. Only condoms are effective.

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57
Candida albicans

Candida albicans is a dimorphic, Gram-positive fungus which exhibits both yeast and filamentous growth. Growth of the organism either on surfaces or in biologic fluids results in an over-budding yeastlike form, measuring 2–3×4–6 mm (Figure 57.1). When the organism invades tissue, both hyphae and pseudohyphae develop (Figure 57.2). They are common in infected tissue.

The female genital tract is a sophisticated microbiological environment. The microbiological presence of an organism does not necessarily equate with the disease. Depending upon age group, geographical location and socioeconomic status, up to 41 % of women may harbor one or more species of candida as a 'normal' constituent of the vaginal flora. Greater than 400 strains of candida have been identified. There is no evidence of vaginotropism. The distribution of strains are comparable between:

(1) vaginal vs. nonvaginal sites; and
(2) patients with candidal vulvovaginitis and with asymptomatic carriage.

If a woman harbors a strain of candida in the vaginal flora, 45% of these individuals will have more than one additional strain of candida present.

While the point prevalence of candidal organisms as constituents of the vaginal flora is significant, it is probable that the principal reservoir for the organism is the gastrointestinal tract. *Candida albicans* can be recovered from 65% of gastrointestinal tract fecal samples in a random population. Patients with vaginal colonization invariably have intestinal carriage of the same organism. Studies in healthy adults suggest that *C. albicans* can be recovered from the oropharynx in 30% of normal adults, from the jejunum in 50%, the ileum in 50%, and the rectum in 60%. Horowitz *et al.* found that the species of yeast found in the vagina of women with recrudescence of vulvovaginal candidiasis is likely to be the same species found in the oral cavity of both partners and in the male ejaculate. In this study, cultures of the oral cavity of the male partner were positive in 36%, ejaculate cultures were positive in 15%, and rectal cultures were positive in 33%. Prostatic cultures failed to reveal a single positive culture. The absence of yeast organism in prostatic fluid and its presence in seminal ejaculate suggests that an untreated reservoir for recolonization exists in the seminal vesicles. Asymptomatic penile yeast carriage occurs in 5–25% of male partners of women with vulvovaginitis candidiasis. The organism can be isolated primarily from the coronal sulcius. The absence of circumcision may not be a critical factor. Horowitz observed comparable rates of penile carriage in circumcised and uncircumcised males.

Oropharyngeal cultures from women with recurrent candidiasis were positive for mycotic organism in 36% of the patients. The oral cavity of the female may be a source for male colonization and subsequent reintroduction of the organism into the vaginal flora. While the incidence of rectal isolation in women with chronic vulvovaginitis is

comparable to that in controlled populations, both oral and vaginal carriage of the organism is elevated in those who have chronic or recurrent disease compared to control groups.

Despite the large number of strains, the spectrum of candidal strains causing vulvovaginitis is limited. The majority of cases are due to *C. albicans*. One-third of the cases are due to *C. tropicalis, C. pseudotropicalis, C. stellatoidea, C. krusei* and *C. guilliermondi*. To cause disease, a given strain of candida must have the ability to attach to squamous epithelial cells. Adhesion can be made between candial organisms and non-biological materials, such as catheters, by electrostatic forces or by complementary receptors and ligands. Non-albicans candida have reduced ability to attach to vaginal epithelial cells.

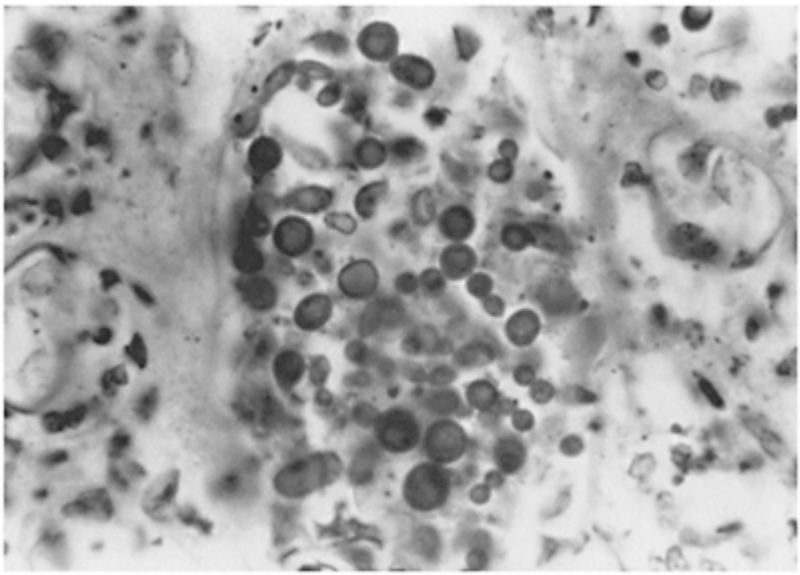

Figure 57.1 *Candida albicans* yeastlike forms. Oval budding yeastlike form growing within the lumen of a renal tubule (PAS×630)

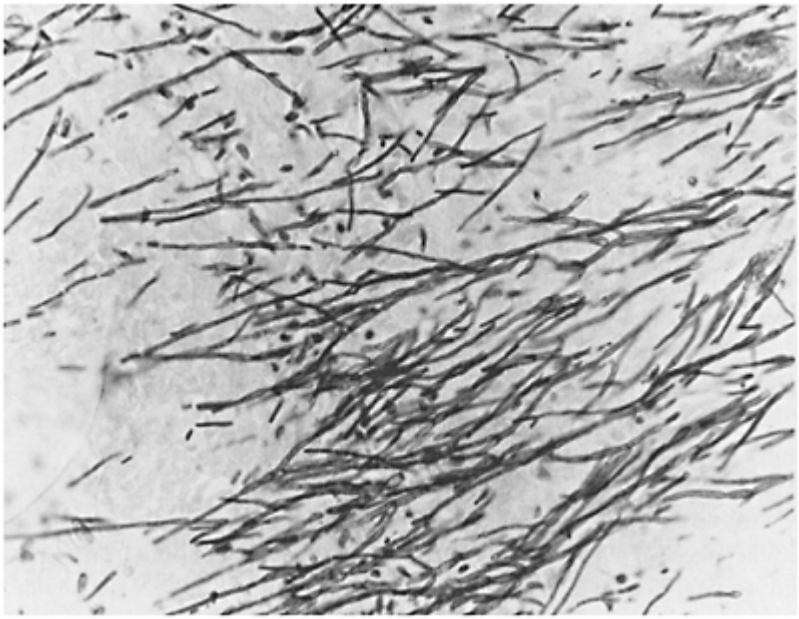

Figure 57.2 *Candida albicans* growing as pseudohyphae within infected tissue (PAS×320)

PATHOGENESIS OF DISEASE

When isolates from patients with recurrent and/or chronic vulvovaginitis candidiasis are compared to isolates from patients with asymptomatic colonization, no differences in attachment avidity have been demonstrated. The principal factors determining disease are: the availability of the organism and some change in the local microbiological environment which permits attachment.

Vulvovaginal candidiasis is rarely a sexually transmitted disease. In more than 85% of the cases, the organism is of endogenous origin. In less than 10% of the cases, sexual intercourse is the probable mode of dissemination.

A demonstrable difference between asymptomatic colonization and vulvovaginal candidiasis is the magnitude of organism replication. Asymptomatic colonization is associated with 10^2–10^5 cfu/ml of vaginal fluid. The emergence of disease from a state of prior colonization is accompanied by a quantitative change in the magnitude of organism replication (greater than 10^6 cfu/ml of vaginal fluid).

Candidal vulvovaginitis is rare in premenarchal and postmenopausal women. The commonest predisposing factors are the glycogen content of vaginal secretions, especially in pregnancy, and moisture. Disease is highest among women living in tropical areas with prolonged high temperature and humidity.

The concept is slowly evolving that for patients with recurring candidiasis who do not have a demonstrable etiological factor; i.e. minor impairment of T-cell functions, the key to reducing the degree of recrudescence of vulvovaginal candidiasis is the reduction of the degree or the eradication of the potential reservoirs. Studies have suggested that by attacking the individual reservoirs, whether oral, seminal, vesical, or intestinal, one can begin to impact on the incidence of recurrence in this group of patients who do not have genesis III type of vulvovaginitis. Intermittent, short-term monthly therapy or persistent low dose daily therapy have both reduced the frequency of recurrences in these kinds of patients. Exactly which therapeutic strategy is most effective awaits scientific confirmation.

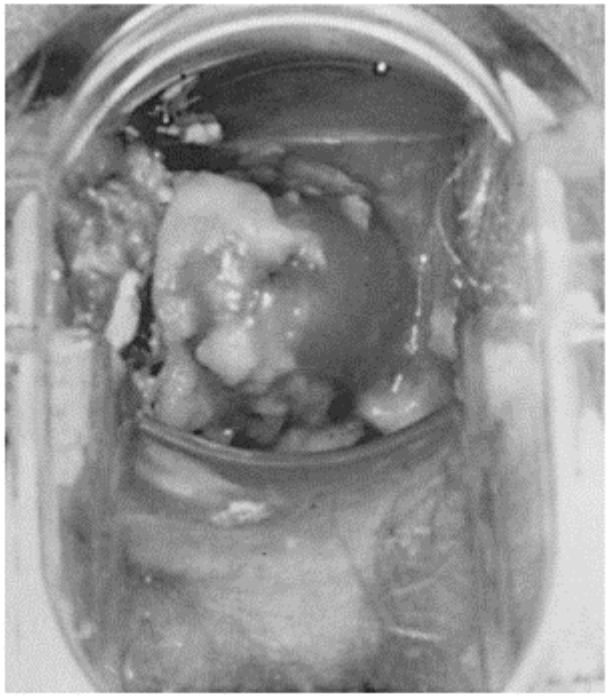

Figure 57.3 Characteristic cottage cheese-like appearance

VULVOVAGINAL CANDIDIASIS

Pruritis vulvae is easily the most prominent symptom of the patient with vulvovaginal candidiasis. Frequently, the itching is intense. Relief may occur during menstrual periods, perhaps due to the alkalinity of menstrual blood. Dyspareunia is a common complaint. Dysuria may result from the passage of urine over the irritated areas. Vaginal discharge is

a variable finding; when present it is practically always preceded by pruritus. Premenstrual exacerbation is characteristic.

Vulvovaginal candidiasis is more a vulvitis rather than a vaginitis. The presence of non-characteristic discharge should alert one to the probability that the etiology of disease may be due to *Trichomonas vaginalis* and not *C. albicans*. When discharge indicative of significant concomitant vaginitis is present, it tends to be relatively sparse in quantity and has a characteristic cottage cheese-like appearance (Figure 57.3). Vaginitis predominating over vulvitis is more characteristic of antibiotic-induced disease.

Table 57.1 Omaha classification of vulvovaginal candidiasis

Genesis I	Primary vulvovaginal candidiasis
	A. Vulvitis
	B. Vulvovaginitis with predominant vulvar involvement
	C. Vaginitis with relatively minimal vulvar involvement
Genesis II	Antibiotic Induced vulvovaginal candidiasis
	A. Secondary to systemic therapy for nonvulvovaginal condition
	B. Ping-pong vaginitis
Genesis III	Systemically influenced vulvovaginal candidiasis
	A. Pregnancy, high dose estrogen contraceptives
	B. Steroids
	C. Diabetes mellitus
	D. T-cell dysfunction
	1. Congenital
	2. Acquired

Pruritis or perineal itching is the symptom of a patient presenting with vulvovaginal candidiasis. The localization of perineal itching is of diagnostic importance. Pruritis limited to the labia majora suggests either cutaneous candidiasis or the presence of ectoparasites. Perineal and vaginal pruritis can be due to either *T. vaginalis*, human papilloma viruses or *C. albicans*. Determination of pH and examination of KOH and saline wet mounts are diagnostic.

The reason for the exacerbation or amelioration of clinical disease in relation to the menstrual cycle is again primarily a function of pH. The pH of menstrual blood is 7.2. *Trichomonas vaginalis* thrives on an alkaline milieu whereas *C. albicans* is relatively inhibited.

Other symptoms may include vaginal soreness, vulvar burning, dyspareunia, and external dysuria. None of these symptoms are specific.

OMAHA CLASSIFICATION OF VULVOVAGINAL CANDIDIASIS

Although candidiasis of the female genital tract is a monoetiological disease, the pathways to pathogenic expression are significantly divergent to constitute a classification scheme for vaginal candidiasis (Table 57.1).

The classification of vulvovaginal candidiasis is composed of three distinct geneses as shown in Table 57.1.

Primary candidiasis

Primary candidiasis has a spectrum of disease whose dipoles are a vulvitis on one hand and a vaginitis on the other. The presence of a clinically significant vulvitis is more characteristic of this group. Augmented moisture/ humidity is its principal catalytic factor. The therapeutic corrollary is the need to concomitantly treat the labia as well as the vaginal reservoir.

Antibiotic-induced candidiasis

Antibiotic-induced candidiasis results from a different alteration of the microbiological environment which is achieved by the eradication of bacterial attachment to mannan and mannoprotein surface antigens. Eradication of the bacteria attached to mannan receptors frees these site for attachment by candida yeast cells.

Just as candida is susceptible to bacteriocins, it is also capable of elaborating bacteriocins which are effective only at an acid pH. Vaginitis is more characteristic of this group than is vulvovaginitis. The major therapeutic goal in treating antibiotic-induced disease is the eradication of the disease in the vaginal reservoir. Preference is given to the tablet form of therapy because of better patient compliance.

Ping-pong vaginitis

Ping-pong vaginitis is a variant of antibiotic-induced candidiasis in which antimicrobial therapy is given for antecedent genital tract infections rather than infections involving another organ system. The classic history of Ping-pong vaginitis is that of a patient improving significantly for a short period of time and then re-experiencing symptoms. A complete re-evaluation of the patient is required in order not to continue prescribing pharmacologically similar drugs which, if anything, aggravate the situation. The most common setting for ‘ping-pong’ vaginitis is a patient with bacterial vaginosis who is treated with oral metronidazole.

Systemically-induced candidiasis

The principal critical factor selecting for systemically-induced candidiasis is an increase in the glucose substrate available in the local microbiological environment or in the presence of T-cell dysfunction for patients with systemically-induced candidiasis due to steroids, diabetes mellitus, or immunodeficiency involving T-cell function.

Intravaginal/vulvar therapy with anticandicidal creams applied topically coupled with perioral fluconazole is preferred.

Pregnancy

Approximately 30% of gravidas have positive vaginal cultures for candida as compared with 16% of nongravid individuals. Reiss has shown that pregnanediol, a steroid hormone produced in large quantities during pregnancy, enhances the growth of *C. albicans in vitro*. Following delivery, the retrogression of the vaginal epithelium and disappearance of glycogen remove the factors enhancing fungal growth. These changes are reflected in a rapid disappearance of candida from the postpartum vagina.

Oral contraceptives

Diddle *et al.* reported on a large series of patients studied over a prolonged period to determine the relationship between oral contraceptives and vaginal candidiasis. They concluded that the incidence of candida vulvovaginitis was more common in women using oral contraceptives for one or more years than in women abstaining from antibirth pills or those taking the medication for less than one year. It should be pointed out, however, that only a limited number of investigators are convinced that a specific relationship exists between oral contraceptives and vaginal candidiasis.

Diabetes mellitus

Diabetes mellitus is usually considered to be one of the conditions that predispose to infection by candida. There is higher frequency of positive vaginal cultures for candida and a greater incidence of vulvovaginitis due to this organism in diabetic than in non-diabetic women.

Diabetes mellitus is thought to act by increasing the glucose substrates available in the local microbiological environment. While an important factor in determining the severity of disease and the incidence of colonization, increased glucose in body excretion or secretion is probably not the critical factor selecting for disease in a given patient. Other than vulvovaginitis, no other form of candidiasis is more common in the diabetic person.

Adrenal steroids

Administration of adrenal glucocorticoids enhances experimental infections due to a variety of microbial agents. Corticosteroids predispose to host cell destruction by stabilizing the lysosomal membrane, thus preventing the release of catabolic enzymes which ordinarily digest phagocytized organisms. This alteration of a primary host defense mechanism results in an increased incidence of both local and systemic candidiasis.

Immunologic disorders

Certain conditions pathogenic for man underscore the importance of cell-mediated immunity in resistance of *C. albicans*. Cutaneous or systemic candidiasis is more likely

to develop in subjects with congenital maldevelopment of the thymus (e.g. thymic dysplasia, thymic alymphoplasia, the fourth pharyngeal syndrome, and retrovirus infection with HIV-1 and HIV-2). Certain families with a genetically determined defect in cellular immunity (characterized *in vivo* by the absence of delayed hypersensitivity and a failure to reject homograph transplants, and *in vitro* by a lack of lymphocyte transformation by candida antigens and the elaboration of a serum factor inhibiting the proliferative response to normal antigen-stimulated lymphocytes) exhibit an exaggerated susceptibility to the organisms. Iatrogenic drug impairment of normal cellular immunity, as reflected by *in vitro* suppression of lymphocyte transformation in response to specific antigenic stimulation, predisposes to candidiasis. Although depression of humoral immunity plays a role in the host's defenses, it is of secondary importance compared to cellular immunity. Disorders of phagocytic function or quantity, defects in phagocytic chemotaxis, phagocyte killing capacities and intraleukocyte metabolism predispose to candidiasis. Among the presenting manifestations of patients with acquired immune deficiency syndrome (AIDS) are vaginal and oropharyngeal candidiasis.

The Centers For Disease Control (CDC) has recently adopted a new classifiction of vulvovaginal candidiasis, based not on pathogenesis, but on potential antifungal selection which divides cases into uncomplicated and complicated. Uncomplicated vulvovaginal candidiasis (mild to moderate, sporadic, non-recurrent disease in a normal host with normally susceptible *C. albicans*) responds to all the aforementioned azoles even as short (<7 days) and single dose therapy. In contrast, complicated vulvovaginal candidiasis (severe local or recurrent vulvovaginal candidiasis in an abnormal host, e.g. an uncontrolled diabetic, and caused by a less susceptible fungal pathogen, e.g. *C. glabrata*) requires longer duration (10–14 days) with either intravaginal or oral azole.

DIAGNOSIS

Speculum examination reveals variable amounts of a thick, white, curd-like or flocculent discharge which is loosely adherent to the vaginal mucosa. The character of the discharge has often been likened to cottage cheese. This type of discharge, while suggestive, is not diagnostic of candida vulvovaginitis. Such a discharge may be physiological. Vaginal and vulvar findings can vary from complete normality of the parts to diffuse vaginal, cervical, and vulvar erythema. In the latter circumstance the vagina may bleed easily on contact, and slight edema of the vulva is common. Cutaneous lesions as an extension from the vagina are not common, but when seen consist of small reddish macules and vesicopustules which may rupture and become secondarily infected. Such 'satellite' lesions are a clue to the etiology of the attendant vaginitis. Excoriation is common due to the intense pruritus.

Determination of pH is one of the most important diagnostic aids (Table 57.2). Patients with candida vulvovaginitis have a pH of 4.2–4.4. Disease usually occurs in the absence of a significant inflammatory response. The presence of >5 WBC/hpf should alert the physician to the possible presence of an additional disease entity. The principal organisms associated with an acid pH are

Table 57.2 Characteristics of candida vulvovaginitis

Clinical presentation	*Discharge*	*pH*	*KOH wet mount*
Pruritis	Sparse, curd-like (cottage cheese appearance)	4.0–4.5	Budding yeast pseudohyphae

C. albicans or group B streptococci (the latter usually functions with a member of the Enterobacteriaceae). While the diagnosis of vulvovaginal candidiasis is suggested clinically by pruritus and erythema in the vulvovaginal area and in some cases the presence of a white, crudy discharge, the diagnosis is made when a wet preparation or Gram stain of vaginal discharge demonstrates yeasts or pseudohyphae, or when a culture or other test yields a positive result for a yeast species.

In deep-seated candidiasis, the presence of pseudohypae necessitates special fungal stains such as the Grocott-Gomori methenamine-silver nitrate stain or PAS staining.

HIV-ASSOCIATED CANDIDIASIS

Candida oropharyngitis/esophagitis is often one of the early AIDS-defining events in women. A women presenting with oropharyngeal candidiasis should be evaluated for possible retrovirus infection. Similarly recurrent vulvovaginal candidiasis is also a potential early marker of disease. The definition for recurrent vulvovaginal candidiasis is four documented episodes in a 12 month period.

CANDIDA-RELATED RECURRENT ALLERGIC VAGINITIS

There is a small group of women with recurrent vaginitis in whom there is an association between coitus and the initiation of pruritis and discharge. The induction of disease may vary depending on the specific male partner. Recent evidence suggests that recurrent vaginitis can arise as a consequence of a transient and localized inhibition of cell-mediated immunity. Lymphocytes from many women with this disorder manifest a reduced *in vitro* proliferative response to *C. albicans*. The inhibition appears to be due to increased production by the patients' macrophages of prostaglandin E, which inhibits interleukin-2 production and thereby blocks lymphocyte proliferation. When lymphocyte responses are impaired, *C. albicans* can readily proliferate and initiate a clinical infection. Prostaglandin E2 production can arise as a consequence of a vaginal allergic response inducing IgE antibodies to *C. albicans,* ryegrass, contraceptive spermicides, and seminal fluid. Medications or chemicals ingested by the male and present in his semen may be transmitted to sensitized females by coitus. Male-specific allergic responses may be induced in females through the seminal transfer of specific IgE antibodies.

The increased realization that recurrent vaginitis may be related to sexual exposure to a specific male will necessitate that semen from the affected woman's partner should be cultured for candida and tested for IgE antibodies reactive with components in his semen or his partner's vaginal secretions.

DISSEMINATED CANDIDIASIS

In obstetrics and gynecology disseminated candidiasis occurs primarily in the context of two clinical situations:

(1) indwelling vascular catheters; and
(2) parenteral nutrition.

Indwelling vascular catheters and needles

The weight of evidence suggests that most systemic candida infections arise from iatrogenic creation of a vascular access through intravenous catheters. A minority of hematogenous infections are secondary to blood vessel invasion from the gastrointestinal tract. Not infrequently, the fungus has been demonstrated in the center of blood clots in thrombosed veins through which infusions had been administered. In reported cases, all obstetric and gynecologic patients developing disseminated candidiasis had received IV therapy, and the majority of these had been managed with large indwelling plastic catheters.

Parenteral nutrition

Candida albicans septicemia is a recognized complication of total parenteral nutrition (TPN) therapy. In a recent summary of the incidence of sepsis complicating TPN, candidemia was found in 3–25% of patients receiving such therapy. Several factors may be involved in the development of fungal sepsis in patients receiving TPN:

(1) Many of the conditions that predispose patients to fungal septicemia (e.g. broad-spectrum antibiotic therapy, radiation, steroid therapy, immunosuppressant therapy) are also present in patients chosen to receive TPN. It is possible that prolonged central venous catheterization coupled with these other variables favors fungal proliferation.
(2) Candida proliferates more rapidly than most common bacterial pathogens in TPN solutions.
(3) Several clinical trials have suggested that ointments containing antibacterial substances applied to polyethylene catheter sites predispose patients to colonization with candida. Since these ointments have been used liberally in the maintenance of TPN catheters, it is conceivable that they have contributed to the increased incidence of fungal septicemia.

CANDIDAL URINARY TRACT INFECTION

The increasing use of corticosteroids, immunosuppressive drugs, antineoplastic agents, and the urinary catheter has led to a significant increase in the prevalence of genitourinary fungal infections. The majority of fungal genitourinary tract infections are either caused by *C. albicans*, one of the other *Candida* species or by *Torulopsis glabrata*.

Cystitis

Candidal cystitis usually occurs in a setting of diabetes mellitus or because of the indwelling use of a Foley catheter associated with antibiotic therapy. Symptoms include nocturia, constant burning and discomfort and an unusual degree of frequency. The urine may be turbid or even bloody. The bladder capacity can be severely compromised. If candida cystitis is suspected, a suprapubic aspirate should be done to rule out fungal infection of the more proximal part of the urinary tract.

Pyelonephritis

Renal involvement may present either as pyelonephritis or with obstructive symptomatology. Candidal infections frequently occur in conjunction with chronic pyelonephritis. There is a tendency for fungal infiltrations of the tip of the papillae which may result in obstruction of the collecting tubules. A bezoar formation with secondary obstructive uropathy may also occur. A temporary diuresis in the course of an otherwise progressive oliguria is said to be diagnostic. Renal or urethral colic may occur with the passage of fungus balls. Other symptoms may be indistinguishable from those of bacterial pyelonephritis. While candida infection may co-exist with concomitant bacterial infection, co-infection with *Proteus spp.* or *Pseudomonas spp.* does not occur.

Evaluation of funguria

Renal involvement occurs in up to 90% of the patients with sustained candidal septicemia. The spectrum of genitourinary candidiasis runs the gamut from asymptomatic candiduria to candidal cystitis to primary renal candidiasis. The major problem is distinguishing true parenchymal involvement from superficial colonization which usually occurs in association with the use of antibiotics and a urinary catheter. In general, the genitourinary tract appears to have considerable ability to rid itself of fungus in the absence of deep-seated infection. The real problem is distinguishing asymptomatic ascending disease from seeding of the urine by established renal disease. Prolonged use of catheterization often delineates a patient who has other potential portals such as central venous lines or hyperalimentation sites which provide excellent alternate sites of infection for candida septicemia.

The diagnosis of genitourinary fungal infection is inferred by the recovery of the agent. When catheterized or suprapubically aspirated specimens in the female are obtained, the incidence of positive urine falls dramatically. A urine culture that is positive

for fungus always calls for confirmation by a properly collected specimen. The definition of funguria is growth of the organism on culture of urine sediments collected on two occasions with an interval of one or more days using proper collection techniques. Cultures of sediment of 10 ml urine centrifuged at 3000 revolutions per minute for three minutes are much more sensitive than ordinary urine cultures and are preferred for diagnosis and the evaluation of therapeutic results. The quantitative colony counts are of little interest and may be misleading since there is no absolute correlation between the degree of funguria and the site or severity of the infection.

To determine the significance of a positive urine culture, blood cultures must be obtained. Renal functions should be evaluated and, if abnormal, an intravenous pyelogram should be done to assess the condition of the upper tract.

Agglutinin titers are of relatively little value because of their inability to distinguish between superficial and deep infections and their frequent cross-reaction with other infections. The candida precipitin titers greater than 1:1 are suggestive of parenchymal infection; however, there is a 7 to 13% false-positive rate. The majority of patients with these false-positive reactions have had mucocutaneous candidiasis associated with autoimmune hypoparathyroidism or hypoadrenalism. The incidence of falsely negative reactions is approximately 12%. These are thought to be due to terminal anergy or the lag phase between the onset of infection and development of precipitin antibodies.

CONGENITAL AND NEONATAL INFECTION

Neonatal candida infection has been documented and studied extensively for many years. While it has only been recently that intrauterine-acquired candidiasis of the fetus and placenta have been recognized, it was not until 1968 that an association between spontaneous abortion and intrauterine fetal infection by candida was first suggested.

Candidiasis acquired *in utero*

Candida infection acquired in *in utero* and clinically manifested at birth is rare.

The most important question to be answered in considering the pathogenesis of intrauterine-acquired candida infection is how the fungus gains access to the fetus and fetal adnexa. Three mechanisms have been postulated.

(1) The most obvious explanation is direct invasion of candida from the vagina to the amniotic fluid following premature rupture of the membranes. Of the 16 cases reported, however, only 4 were associated with premature rupture of the membranes (PROM). In 10 cases, the membranes ruptured during labor or parturition and the infant subsequently evidenced disease that was clearly established well before the onset of labor. In 2 cases of documented intrauterine acquired infection, the infant had been delivered by cesarean section with membranes intact at the time of the procedure. Thus the association of PROM with placental and fetal candidiasis cannot be documented in the majority of cases reported in the literature.

(2) Benirschke and Raphael postulate the existence of subclinical, self-healing ruptures in the membranes through which *C. albicans* may enter the amniotic sac. The difficulty of unequivocally proving this mechanism is obvious.

(3) Penetration of *C. albicans* through intact membranes is a third possibility. It has been shown that *C. albicans* is able to penetrate and infect the chick chorioallantoic membrane and to kill the embryo by invading its internal organs. It is also conceivable that local areas of inflammation or other insidious pathologic changes may render the intact fetal membranes more permeable to fungi. The report of two cases of congenital candidiasis following repeated amnioscopy suggests that trauma to intact membranes may play a role as well.

Regardless of the primary mechanism of the fetal membrane invasion, once the amniotic fluid is infected with *C. albicans,* involvement of the fetal skin, surface of the umbilical cord, fetal bronchi, and fetal gastrointestinal tract becomes almost inevitable.

The lesions resulting from intrauterine-acquired candida infection have been well described by Aterman. The gross appearance of the umbilical cord is normal to cursory inspection, but upon careful examination, barely perceptible discrete, variable, yellowish white lesions are seen irregularly scattered over the epithelial surface. They are flat and mostly of pinpoint size. Histologically, the surface of the cord may be covered by a mycelium of hyphae, or hyphae may have penetrated into the substance of the cord. Penetration into the substance of the Wharton's jelly is never deep, according to Aterman, owing to the intense inflammatory response elicited by the invading candida. As a result of the invasion of the cord by candida, an effusion of fetal leukocytes through the large vessels occurs, and the so-called candida granulomas develop. They are characterized by foci of necrotic Wharton's jelly containing much nuclear debris, surrounded by pyknotic cell nuclei belonging to polymorphonuclear leukocytes and mononuclear cells within and around the granuloma. At the periphery is a gradual transition toward otherwise normal jelly permeated by varying numbers of migrating inflammatory cells. Interestingly, there appears to be an inverse relationship between the ease with which candida organisms can be seen and the stage of development of the inflammatory response.

Gross pathologic findings in infants contracting candidiasis *in utero* consists of multiple petechial hemorrhages in the thymus, heart, and adrenals. Histologically, yeast forms without an associated inflammatory reaction have been described in the alveolar spaces. Both yeast and mycelial elements have been demonstrated in the lumen of the bowel. Pathologic findings may be confined exclusively to the skin (congenital cutaneous candidiasis), with widespread, diffuse, macular, papular, vesicular and pustular eruptions and exfoliation. Microabscesses of the skin and paranychia have been reported.

Prematurity is a common finding in infants acquiring candida infection *in utero*.

SPONTANEOUS ABORTION AND FETAL CANDIDIASIS

In 1968 Schweid and Hopkins reported the first case of spontaneous abortion associated with fetal candida infection. Their patient was a 19-year-old primipara who had had an intrauterine contraceptive device (IUD) (Lippe's loop) in place for 13 months. She spontaneously aborted a 69-mm fetus at 13 weeks' gestation. There was no history of maternal candidiasis or other infection. Examination of the conceptus revealed an inflammatory exudate in the chorionic plate which did not extend into the amniotic sac, chorionic villi, or decidua. The inflamed chorion adjacent to the amniotic sac contained a

heavy growth of blastospores and pseudohyphae characteristic of candida. No other organisms were demonstrated.

Another case report associating fetal candida infection with spontaneous abortion is that of Ho and Aterman. Their patient was a 32-year-old multigravida who had had an IUD in place for 15 months. At 14 weeks' gestation, she spontaneously aborted a 75 g fetus, 11 hours after rupture of the membranes had occurred. Microscopic examination revealed fungi and typical lesions in the fetal membranes, lungs, and gastrointestinal tract.

The source of infection in these two cases is obscure, but the same possibilities seem to exist as were previously described for intrauterine-acquired neonatal candidiasis. It is known that in cattle, in which fungi have also been implicated as a rare cause of abortion, it is possible to isolate organisms previously injected into the maternal circulation from calves or abortuses postpartum. This raises the further possibility of a hematogenous source of infection.

That both patients had IUDs in place for more than a year is intriguing. Schweid and Hopkins have suggested that the altered local environment induced by the IUD might well have fostered the infection caused by this opportunistic fungus. It is also interesting to speculate on the relationship between the candidiasis and the occurrence of the abortion. The common occurrence of premature labor in cases of intrauterine-acquired candida infection has already been mentioned. Ho and Aterman argue that, if candida can precipitate premature labor, it may occasionally provoke abortion as well.

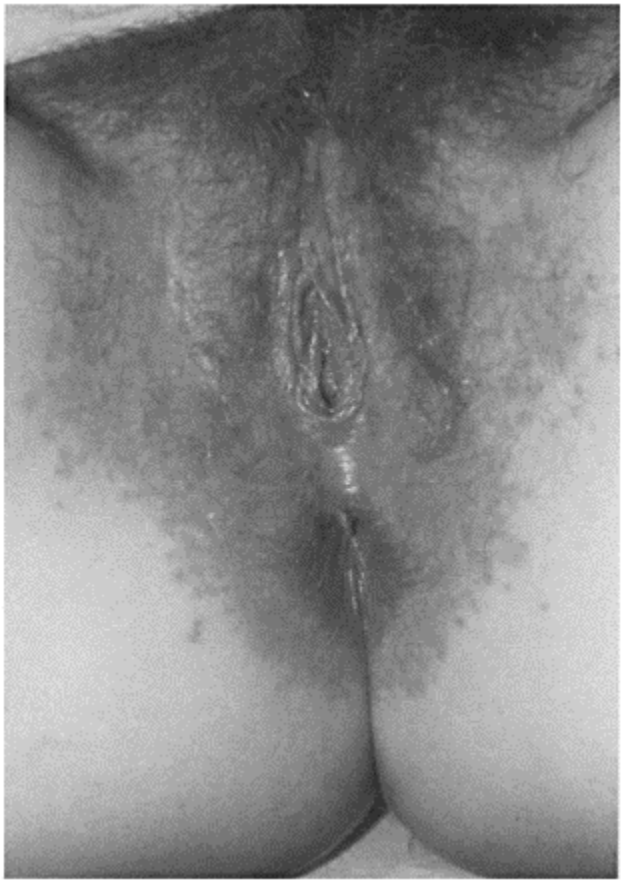

Figure 57.4 Cutaneous extension of vulvovaginal candidiasis due to *Candida albicans* mixed with hypersensitive reaction

SIGNIFICANCE OF CANDIDEMIA

One of the most difficult problems is determining the biological significance of the recovery of candida from the intravascular compartment of seriously ill patients.

Recovery of a *Candida* species from the blood requires the differentiation of self-limited infection associated with an intravenous cannula from systemic candidiasis. Factors suggesting the latter condition are:

(1) development of macronodular skin lesions in a febrile patient;
(2) concomitant demonstration of candiduria;

(3) development of endophthalmitis;
(4) presence of classic physical findings of infectious endocarditis;
(5) embolization to medium-sized arteries of the extremities, brain, lungs or mesentery;
(6) persistent candidemia after removal of all intravenous arteries;
(7) use of oral hyperalimentation in a patient with some underlying defect in the gastrointestinal tract or in host defense mechanisms;
(8) development of osteomyelitis, meningitis, pyelonephritis or arthritis; and
(9) occurrence in an intravenous drug abuser or immunosuppressed individual receiving intravenous hyper-alimentation.

While a presumptive diagnosis may be inferred from one of the above, a definitive diagnosis requires demonstration of the organism within a distant organ system. Biopsy and culture of the macronodules should prove the presence of *Candida* species. About 5% of patients develop an endophthalmitis within 1–6 weeks following candidemia. These patients complain of orbital or periorbital pain, blurred vision and scotoma. On ophthalmoscopic examination, white glistening exudates, sometimes with a ray-like appearance involving the retina and choroid, can be visualized if embolization to medium sized arteries has occurred. The keys to diagnosis of disseminated candidiasis are either persistent candidemia after removal of an intravenous catheter or presence of candidal precipitins in serum. A titer of candida precipitins exceeding 1:8 by counterimmunoelectrophoresis or a rising titer infers the diagnosis of disseminated candidiasis.

THERAPY OF VULVOVAGINAL CANDIDIASIS

Genesis I—Primary

Primary candidal vulvovaginitis is not a totally homogenous disease entity. It is a spectrum of disease whose dipoles are a vulvitis on one hand and a vaginitis on the other. The distinction between those situations in which vulvitis is greater than vaginitis from those cases in which vaginitis is greater than vulvitis is of more than academic importance. Total reliance on intravaginal medication in cases with significant vulvitis is associated with frequent therapeutic failures. If vulvitis is clinically significant, simple eradication of the vaginal reservoir will not afford relatively prompt relief of symptoms nor a one standard deviation probability of a microbiological cure. The physician must concomitantly treat for vulvitis. This is best achieved through direct application of medication to the perineum and vulva and restriction of undergarments to loose-fitting cotton pants.

If there is anorectal extension of disease, this is one situation where the topical use of perioral nystatin may be warranted. It is NOT necessary in primary vulvovaginal candidiasis to attempt eradication of the intestinal reservoir. While the probable source of initial vaginal colonization, the presence of the organism in the gastrointestinal tract is not the cause of a disease state. A critical change in the microbiological environment must occur for colonization to become a disease state. Increased moisture appears to be the most important catalytic factor in genesis I type of disease.

Current effective therapies for genesis I and II are listed in Table 57.3.

Preparations for intravaginal administration of butaconazole, clotrimazole, miconazole, and tioconazole are now available over-the-counter (OTC), and women with vulvovaginal candidiasis can choose one of those preparations. The duration for treatment with these preparations may be 1, 3 or 7 days. Self-medication with OTC preparations should be advised only for women who have been diagnosed previously with vulvovaginal candidiasis and who experience a recurrence of the same symptoms. Any woman whose symptoms persist after using an OTC preparation should be counseled to seek medical care.

Genesis II—antibiotic-induced candida vaginitis

Why do antibiotics induce candidiasis? The antibiotic, to induce candidiasis, must alter the microbiological environment through the eradication of the principal

Table 57.3 CDC 2002 regimens for candidal vulvovaginitis

Oral agent:
Fluconazole 150 mg oral tablet, one tablet in single dose

Intravaginal agents:

Butoconazole 2% cream 5 g intravaginally for 3 days;*† and sustained release cream intravaginally single application

or
Clotrimazole 1% cream 5 g intravaginally for 7–14 days;*†

or
Clotrimazole 100 mg vaginal tablet for 7 days;*†

or
Clotrimazole 100 mg vaginal tablet, two tablets for 3 days;*

or
Clotrimazole 500 mg vaginal tablet, one tablet in a single application;*

or
Miconazole 2% cream 5 g intravaginally for 7 days;*†
or

or
Miconazole 200 mg vaginal suppository, one suppository for 3 days;*†

or
Miconazole 100 mg vaginal suppository, one suppository for 7 days;*†

or
Nystatin 100000-U vaginal tablet, 1 tablet for 14 days.

or
Tioconazole 6.5% ointment 5 g intravaginally in a single application;*†

or
Terconazole 0.4% cream 5 g intravaginally for 7 days;*

or
Terconazole 0.8% cream 5 g intravaginally for 3 days;*

or
Terconazole 80 mg vaginal suppository, 1 suppository for 3 days.*

*These creams and suppositories are oil-based and may weaken latex condoms and diaphragms. Refer to product labeling for further information.
†Over-the-counter (OTC) preparations.

anaerobic bacteria which govern pH. The inhibitory effects of bacteriocins and bacteriocin-like products are pH dependent. The eradication of selective bacteria, especially anaerobes, in selected cases, free candida from their replicative constraints.

Antibiotic-induced vulvovaginal candidiasis manifests as primarily a vaginitis when the magnitude of replication exceeds 10^6 cfu/ml of vaginal fluid and the candida revert to their tissue invasive dimorphic form. Vaginitis is more characteristic of this group than is vulvitis.

In antibiotic-induced disease, the major goal is the eradication of the vaginal reservoir. If the vaginal reservoir is eliminated, unless a concomitantly significant vulvitis is present, the problem will cure itself.

Genesis III—systemically influenced candidiasis

The critical factor selecting for systemically-induced candidiasis is an increase in the glucose substrate available in the local microbiological environment or T-cell dysfunction. Patients with chronic candidiasis appear to have reduced responsiveness to candidal antigen. Hyporesponsiveness may be induced by the disease itself and may not be due to a pre-existing condition. For patients with systemically-induced vulvovaginal candidiasis due to steroids, diabetes mellitus, or immunodeficiency involving T-cell function, intravaginal/vulvar therapy with anticandicidal creams topically applied coupled with perioral ketoconazole or fluconazole is preferred. It is imperative to treat the underlying condition aggressively or change the physiological status, i.e. pregnancy. Candidiasis associated with poorly controlled diabetes will relapse unless the problem in carbohydrate metabolism is brought under control.

Fluconazole, itraconzole and ketoconazole are oral antimycotic agents which are effective against candida vulvovaginitis. They are thought to affect sterol metabolisms in yeast and fungal cells resulting in the accumulation of 14 alphamethyl sterols which are known to disturb membrane and cell properties. There is an intracellular build-up of peroxide which is thought to contribute to cell death.

In clinical studies, a single oral dose of fluconazole (200 mg) has been as efficacious as oral ketoconazole (200 mg daily for six days) or intravaginal clotrimazole in the treatment of simple vulvovaginal candidiasis.

Owing to its low molecular weight, affinity for plasma proteins and water solubility, itraconazole is readily absorbable following oral or intravenous administration. The drug diffuses into cerebrospinal fluid and is actively eliminated in urine.

The use of oral antimycotics for vulvovaginal candidiasis has largely been blunted by the potential adverse drug reactions associated with ketoconazole. Systemic

hepatotoxicity occurs in 1/10000 to 1/15000 patients taking ketoconazole. Transient minor elevation of levels of liver enzymes occurs in 5–10% of patients taking the drug. At least four fatal cases have been reported which occurred despite discontinuation of ketoconazole to inhibit adrenal steroidogenesis which may result in gynecomastia and in rare instances, hypoadrenalism.

Clinically important interactions may occur when some of the oral agents are administered with other drugs, including astemizole, calcium channel antagonists, cispride, coumarin-like agents, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.

CONSEQUENCES OF VULVOVAGINAL CANDIDIASIS FOR THE MALE

Two types of disease occur in male consorts: one group develops a specific candida balanoposthitis. A second group presents with an allergic balanoposthitis presumably due to hypersensitivity to candida antigens. The condition may be more common than is generally recognized. Diddle *et al.* found balanoposthitis in more than 10% of the husbands of the 225 women with candida vaginitis in their series.

Hypersensitivity reaction is distinguished from balanitis in that the reaction begins within hours after sexual intercourse. Itching is most commonly the initial manifestation. The goal is to eliminate penile carriage as well as eradicate the oral cavity and seminal vesicles reservoirs. Post-coital suppressive prophylaxis is indicated for the male when institution of personal hygiene is not accepted or chronic candidal seminal vesicle involvement is documented.

RECURRING CANDIDIASIS

Sobel conducted a prospective placebo controlled study of 74 women with recurrent vulvovaginal candidiasis who were treated with oral ketoconazole (400 mg daily for two weeks) and then were randomly assigned to receive placebo, prophylactic ketoconazole 400 mg daily for five days beginning with the onset of the menses for six cycles or low-dose ketoconazole 100 mg daily for six months. Within a six month follow-up, 15 of 21 women (71.4%) treated with placebo had symptomatic recurrences of candida vaginitis. In contrast, candida vaginitis occurred in only 6 of 21 (28.6%) and in 1 of 21 (4.4%) of the women in the short-course and continual drug groups. While the maintenance prophylaxis with oral ketoconazole was effective in preventing recurrent episodes of vulvovaginitis, relapse was extremely common after the withdrawal of drugs.

The problem with the use of ketoconazole is that the drug is not totally benign. Symptomatic hepatotoxicity occurs in some patients taking ketoconazole with an incidence between 1:10000 and 1:15000. Toxicity is usually hepatocellular but may be cholestatic or both. Hepatoxicity is usually reversible when ketoconazole is discontinued, but at least four fatal cases have been reported, two of which occurred despite discontinuation of ketoconazole after the onset of symptoms. Transient minor elevations of liver enzymes in serum are not necessarily predicted for the toxicity. This phenomenon

occurs in 5–10% of patients taking the drug. Liver function tests should be monitored before therapy, every other week for two months during the initial therapy and monthly during the remainder of therapy. The use of the drug should be stopped when significant elevations of liver enzymes are detectable or when signs and symptoms of hepatitis are noted.

A previous study by Davidson and Mould showed that intermittent monthly prophylaxis with vaginal clotrimazole cream and tablets given on the fifth and eleventh day of the menstrual cycle significantly reduces the rate of clinical recurrences compared with placebo. If periodic eradication of vaginal and oral carriage of *C. albicans* is shown to be a valid approach, it should be achieved with a drug which is justifiable in terms of risk—benefit ratios.

CANDIDA GLABRATA (TORULOPSIS)

Candida glabrata is a small oval yeast belonging to the family *Cryptococcoceae*. Like *Candida albicans*, it may be a constituent of the biological flora of skin, oropharynx, genitourinary tract and gastrointestinal tract of man. It grows preferentially in the presence of air and in so doing produces blastospores rather than pseudohyphae or ascospores.

The organism is thought to be a symbiont of man; however, similar factors which select for disease with *C. albicans* also permit *C. glabrata* to function as an opportunistic pathogen. Certain conditions have been found in association with the pathogenic potential of the organism. These include:

(1) previous antibiotic therapy;
(2) indwelling intravenous catheter and/or hyperalimentation therapy;
(3) radiotherapy;
(4) chemotherapy;
(5) immunosuppressive therapy including steroids; and
(6) diabetes mellitus.

Candida glabrata can function as both a local and systemic pathogen. Both fungicemia and endocarditis have been reported. The organism can produce a histological pattern which resembles *Histoplasma capsulatum*.

Vulvovaginitis

Vaginal torulopsis does not compare in intensity with the discomfort induced by vulvovaginal candidiasis. The pruritis or burning tends to be markedly less. Because of its minimal cytotoxic effect, leukorrhea tends to be scant. There is no tendency to clumping or creation of vaginal plaques. Rarely is dyspareunia or burning on the initiation of micturition present. The vaginal pH remains acidic, varying between 4.0 and 4.5. The lactobacilli associated with a simplified bacterial flora are usually present in cases of vaginal torulopsis. Mixed infections are rare.

Diagnosis

Examination of wet mount preparations reveals spores of variable size (two to eight microns) with unilateral germination which occur singly or group in cumuli. Gram staining reveals Gram-positive spores of variable size with unilateral germination which tend to form small cumuli in the form of brancus. In contradistinction to *C. albicans*, the leukocytes may exhibit a tendency to phagocytize the spores of *C. glabrata*. In cases of *C. glabrata* fungicemia, the organism can occasionally be identified in smears of buffy coat of blood.

The organism grows readily on Sabouraud's dextrose agar where it produces smooth, glistening, pasty-white colonies. With time they become grayish-brown. An Indian-ink preparation fails to demonstrate a capsule. Neither pseudohyphae nor ascospores are identifiable. Blastospores can be demonstrated on rice plates. Definitive diagnosis is achieved by demonstrating fermentation of glucose and trehalose and not maltose, sucrose, lactose, galactose, urea and potassium nitrate.

Therapy

Drugs like clotrimazole achieve their fungistatic efficacy primarily by inhibition of demethylation of 4, 4, 14-trimethylsteroids. When the imidazoles are used in the therapy of *C. albicans*, the ersosteril precursor accumulates, whereas with *C. glabrata*, lanosterol accumulation occurs. Apparently in *C. glabrata*, side-chain alkylation proceeds after demethylation reactions. The variable success attained with intravaginal imidazoles effective against *C. albicans* is thought to be due to failure to eradicate coinfection of the urinary tract and subsequent reinfection from this source.

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Coccidioides immitis

Coccidioides immitis is a pathogenic saprophyte with a dimorphic mode of growth in man and in the soil. In exudative lesions of man, it exists as a spherical thick-walled endospore filled with an organism called a spherule. The spherule measures 40–70 μm in diameter. When it ruptures, the spores are released, and each in turn repeats the replicative cycle. In culture the fungus develops a mole-like configuration identical to its growth in soil. The pathogenic form is non-contagious for humans. Infection is contingent on the development of arthrospores by the hyphae and their subsequent inhalation or inoculation.

In North America, *C. immitis* is endemic in the lower southern region which includes some parts of south-western United States and northern Mexico. There is a high prevalence of disease ('Valley fever') in the San Joaquin valley of California.

IMMUNOLOGY OF INFECTION

Cultivation of the fungus in a liquid medium results in the elaboration of an immunologically specific polysaccharide, coccidioidin, which may be used as the source of antigen for:

(1) skin testing;
(2) immunodiffusion; and
(3) complement fixation.

Antibodies against the mycelial phase antigen develop in response to acute infection with *C. immitis* within one to three weeks after the onset of disease and disappear within four months. These antibodies can be demonstrated by tube precipitin, latex agglutination or immunodiffusion methods. Complement-fixing antibody titers usually indicate a high probability of dissemination. Sixty-one percent of patients have titers greater or equal to 1:32. The complement-fixing antibody titer parallels the activity of the disease. A rising titer while a patient is on therapy is a poor prognostic sign. Counterimmunoelectrophoresis appears to be as sensitive and specific as complement-fixation testing.

The development of a delayed type of hypersensitivity can be demonstrated by a tuberculin-like reaction secondary to the intradermal injection of coccidioidin. When the area of induration exceeds 5 mm in diameter, the reaction is interpreted as indicative of prior antigenic stimulation. The onset of delayed hypersensitivity occurs within a few days to two weeks after the onset of disease and usually before serological evidence of infection occurs. Once delayed hypersensitivity to the organism is acquired, the individual (barring significant changes in his immunologic status) is basically immune to

exogenous reinfection. There is a low degree of cross-reactivity with antigens derived from *Histoplasma, capsulatum* and *Blastomyces dermatitidis*. Anergy is common in disseminated coccidioidomycosis.

CLINICAL MANIFESTATIONS

Coccidioidomycosis is a dust-borne disease of the arid regions of southern California, Nevada, Arizona, and the western part of Texas. It is one of the most important fungus-produced diseases in the western United States. The peak incidence of infection has a seasonal distribution and coincides with those months in which rainfall is lowest. The infection is most frequently the consequence of air-borne dissemination of infectious material for which the respiratory tract functions as the portal of infection.

Approximately 100000 cases of coccidioidomycosis occur each year in the United States. Disease is an iceberg phenomenon relative to infection. Even when disease occurs, the great majority of cases are not properly diagnosed.

The organism grows in nature, producing fragile aerial hyphae with highly infectious chlamydospores. Transmission is by inhalation of the fungal spores. The fungus reproduces in animal tissues by endosporulation and consequently person-to-person transmission does not occur. In rare instances, skin abrasions have permitted the establishment of infection.

After an 8- to 14-day incubation period, disease, if it is to be manifested, does so. In approximately 30–50% of infected individuals, a clinical pattern evolves which ranges from a mild influenza-like syndrome to one characterized by chills, fever, malaise, myalgia, a cough that is often associated with a pleuritic component, and night sweats. A small number of persons at this time develop erythema nodosum. Annual incidence rates are highest for males and individuals over the age of 65 years.

In approximately 0.2% of infected individuals, systemic dissemination occurs. Extrapulmonary lesions characteristically develop as a progression of the initial infection. All organ systems are potential sites of involvement, although there seems to be a predilection for skin, the reticuloendothelial system, bone, and the central nervous system. The tissue response is one of granuloma formation in which typical endosporulating spherules may be identified within a multinucleated giant cell. Dissemination of the organism carries with it a poor prognosis. The probability of dissemination and consequently of morbidity and mortality is greater in dark-skinned individuals, whereas limited infection is more likely in Caucasians.

Like tuberculosis, both disease and female genital tract involvement may be due to reactivation of previously disseminated infection.

The incidence of infection/disease is regionally increasing in immunocompromised individuals. The probability of overt coccidioidomycosis in patients with AIDS is significantly increased. Bylund *et al.* reported a case of female genital tract coccidioidomycosis and coccidioidal peritonitis which developed after chemotherapy for Hodgkin’s disease.

FEMALE GENITAL TRACT INVOLVEMENT

Coccidioidomycosis affects one in every 1000 pregnancies in endemic areas of the southwestern United States. Female genital tract involvement is a rare manifestation of disseminated coccidioidomycosis. Coccidioidomycosis of the female genital tract is usually manifested as granulomatous endometritis and/or granulomatous tubo-ovarian disease with peritonitis. The patient usually presents with secondary infertility, recurrent pelvic pain, or a history of repeated pelvic infection refractory to conventional therapy. The last presentation usually occurs in conjunction with fever or a significant vaginal discharge.

With advanced disease, in addition to fever and leukocytosis, the patient may exhibit, on a pelvic examination, marked tenderness involving the adnexa and above all the cul-de-sac. Disease is usually bilateral. Not infrequently, a tubo-ovarian complex is present. At laparotomy, miliary granulomatous nodules can be discerned involving the omentum, peritoneum, and serosa.

As in genital infection with *Mycobacterium tuberculosis,* the fallopian tube is the probable site of initial metastatic infection and bears the brunt of the disease process. While pelvic coccidioidomycosis is usually associated with coccidioidal peritonitis, fallopian tube disease can result in both endometrial disease and serosal involvement. Histologic analysis reveals a diffuse chronic interstitial inflammatory response with focal areas of granulomatous involvement characterized by epithelial cells, rare giant cells, and coccidioides spherules. The occurrence of coagulative necrosis is not uncommon.

There is usually no evidence of disease elsewhere. Chest roentgenograms are negative or may indicate old disease. The absence of concomitant disease has implied the probability that, as with *M. tuberculosis* infection, genital involvement is the consequence of hematogenous dissemination at the time of the initial pulmonary infection and subsequent endogenous activation at a later date. The latent period during which endogenous reinfection may occur may be up to 8–10 years.

Pelvic coccidioidomycosis appears to be a distinct entity and not merely a concomitant involvement associated with systemic dissemination. Huntington *et al.,* in a review of 142 autopsy cases of acute fatal coccidioidomycosis, could not identify a single instance of involvement of the female genital tract. Similarly, there were no documented cases of pelvic infection due to *C. immitis* in the study of 40 cases of disseminated coccidioidomycosis seen at Kern General Hospital from 1965 to 1972. These patients may not have survived long enough for genital tract disease to have evolved. Saw *et al.* demonstrated the presence of granulomatous coccidioidal endometritis at six weeks postpartum in a 22-year-old Mexican woman with disseminated coccidioidomycosis. She had delivered a premature baby who died at three weeks of age from disseminated coccidioidomycosis.

Of the 11 patients described by Bylund *et al.,* seven had tubo-ovarian coccidioidomycosis and coccidioidal peritonitis; two of the seven had concomitant coccidioidal endometritis. The other four patients had coccidioidal endometritis, two as part of generalized coccidioidomycosis and two as apparently localized endometritis.

The seven patients with tubo-ovarian coccidioidomycosis and coccidioidal peritonitis all had chronic abdominopelvic pain. Three patients without endometritis had vaginal discharge; the two patients with concomitant endometritis had palpable adnexal or cul-de-sac disease.

Since the spherules are non-infectious for humans, infection of the sexual consort is not a clinical consideration.

COCCIDIOIDOMYCOSIS COMPLICATING PREGNANCY

Pregnancy alters the natural history of coccidioidomycosis. Pregnant patients with infection/disease develop dissemination and serious disease more than the general population. Whereas the incidence of dissemination in immunocompetent individuals is markedly less than 1%, that observed in pregnant women has been 40 to 100 times the rate observed in the general population. Caldwell *et al.* reported 32 cases of infected women who delivered live borne infants or aborted in the 1993 California epidemic. Disseminated disease occurred in three of the 32 cases. Based on their review of 61 cases of coccidioidomycosis in pregnancy, Arsura *et al.* have contended that the occurrence of erythema nodosum is a salient marker of a positive outcome for pregnant women.

In endemic areas coccidioidal infection may be one of the leading causes of maternal mortality. Manifestation of coccidioidomycosis in pregnancy may include pain and swelling of knees, ankles, or wrists. In pregnant patients, both the incidence of dissemination and its resultant mortality rise markedly.

Prior to amphotericin B therapy, systemic dissemination in non-pregnant patients was associated with about a 50% mortality. When coccidioidomycosis complicates pregnancy, the problem is that of potential maternal mortality as a consequence of disseminated disease. Maternal mortality as well as possible fetal involvement is related primarily to whether or not disease becomes disseminated.

The interim between initial infection and dissemination may be prolonged; this circumstance, however, tends to be the exception, not the rule. About 10% of patients with non-disseminated coccidioidomycosis (even if acquired several months prior to conception) may have subsequent dissemination during pregnancy. In its usual non-disseminated form, infection during gestation does not significantly alter the pregnancy; maternal mortality is related primarily to whether or not the disease becomes disseminated.

INVOLVEMENT OF THE PRODUCTS OF CONCEPTION/CONGENITAL INFECTION

Placental coccidioidomycosis

Placental coccidioidomycosis without necessarily fetal involvement is well documented. Harris reported seven cases of placental involvement of coccidioidomycosis. Smale and Waechter identified three additional cases in which placental involvement occurred during systemic dissemination. In this series, only one probable case of congenital

coccidioidomycosis was identified. The infant was born prematurely and died of coccidioidomycosis when 29 days old. A matter of speculation is whether the infrequency of congenital infection is a reflection of the probable limitations of infection to the placenta because of either:

Table 58.1 Recommended therapy for severe primary or incipient coccidioidal dissemination

Drug of choice	***Dosage***
Amphotericin B	1.0–1.5 mg/kg/day tapering to 1.0–1.5 mg/kg three times a week to a total dose of 0.5–1.5 g (IV)

(1) the size of the coccidioidal spherules, resulting in their physical exclusion from the fetal circulation; or
(2) the severity of the host reaction, resulting in thrombosis of the adjacent vascular spaces and an acute inflammatory response.

Nickisch *et al.* demonstrate normal umbilical artery velocimetry in the only case of coccidioidal placentitis appropriately studied to date.

Congenital coccidioidomycosis

Congenital disease does occur but is rare. In Smale and Waechter's series of 15 cases of disseminated coccidioidomycosis during gestation, fetal loss approached 50%. This loss was primarily due to prematurity or fetal death *in utero* secondary to maternal death. The women who survived to term did not experience excessive fetal loss.

The prime obstetric problem is how to treat the gravida who develops non-disseminated coccidioidomycosis. Because of the 10% chance of dissemination, which carries at least a 90% mortality rate in the recent past if the infection is left untreated, these patients must be closely followed for:

(1) a rising antibody titer; or
(2) roentgenographic evidence of pulmonary involvement.

Changes in either of these parameters require immediate institution of systemic therapy.

Similarly, the finding of placental coccidioidomycosis at parturition is deemed prima facie evidence of dissemination and hence dictates the institution of immediate therapy.

The regimen of amphotericin B is the same as that for the non-pregnant woman. Chemotherapy appears to enhance survival. The fetal outcomes of women treated with amphotericin B have been reasonably good.

DIAGNOSIS

Infection/disease

The diagnosis requires a high index of suspicion in endemic areas and may be inferred either from the demonstration of delayed hypersensitivity to coccidioidin or the presence in the serum of complement-fixing or precipitating antibodies. Most patients with genital tract involvement will have a titer of 1:16 or greater.

In cases of disseminated disease with pulmonary involvement, coccidioides spherules can be identified in fewer than 1/3 of the cases by direct examination of the sputum. Cultures of sputum are diagnostic in approximately 2/3 of cases; however, they are highly contagious to laboratory personnel and require special handling. When scalene node lymphadenopathy is present, biopsy is almost invariably diagnostic. A definitive diagnosis is contingent on the demonstration of the organisms in either tissue exudate, biopsy material, sediment of sputum or gastric washings; or inoculation of such material onto an appropriate growth medium or into the peritoneal cavity of mice, with the subsequent isolation of the organism.

Genital tract involvement

The prerequisite for diagnosis of pelvic coccidioidomycosis is a knowledge concerning potential genital tract involvement and a high index of suspicion in patients from endemic areas presenting with some combination of fever, recurrent pelvic pain, vaginal discharge, infertility, menstrual aberration, or a history of recurrent pelvic inflammatory disease (refractory to the usual mode of therapy). The finding of nodularity in the cul-de-sac in association with evidence of an acute inflammatory process may alert one to the possibility of pelvic coccidioidomycosis.

Not infrequently, the diagnosis is not suspected until laparotomy. The presence of widespread miliary involvement of the omentum, serosa, and peritoneum, in conjunction with significant adnexal pathology, renders the process indistinguishable from that due to *M. tuberculosis*. The need to make the diagnosis at the operating table is underscored by the fact that therapy for genital tuberculosis is medical, whereas pelvic coccidioidomycosis is best dealt with by surgical resection. Wet mounts of the peritoneal fluid can usually demonstrate the spherules of *C. immitis*.

Confirmation can be achieved with culture techniques or histologic analysis. The complement-fixation text for *C. immitis* is positive. This test should be a routine part of any infertility work-up in an endemic area. The value of the test is not in its being positive, but rather in its use for excluding the disease entity from the differential diagnosis.

The magnitude of disease and the age and condition of the patient may influence the extent of surgical resection. In most cases, the operative procedure of choice is total abdominal hysterectomy and bilateral salpingoophorectomy.

THERAPY

Coccidioidomycosis was the leading cause of maternal deaths at Kern General Hospital in California from 1950 to 1966. Because the disseminated disease mortality in pregnancy approached 100%, it was recommended that all such patients be treated with amphotericin B (Table 58.1). The indications for therapy are as follows:

(1) persistent fever, prostration, elevated blood sedimentation rate, with considerable pulmonary involvement and hilar adenopathy;
(2) unstable serology; that is,

   (a) a rising titer of complement fixation above 1:64 dilution; or
   (b) persistent precipitins.

(3) evidence of spread from a primary pulmonary focus, including invasion of *C. limmitis* of lymphatic, cutaneous, skeletal, cardiac, genitourinary, and meningeal systems or the pleuroperitoneal space;
(4) weak or negative skin reaction to coccidioidin;
(5) member of susceptible group; that is, black, Filipino, or Mexican;
(6) Certain metabolic events, including

   (a) pregnancy; and
   (b) diabetes mellitus.

Fully effective therapy for disseminated coccidioidal disease requires not only the use of amphotericin B and other antimicrobials, but also the application of established surgical principles-drainage of abscesses, removal of infected bone, excision of sinuses, etc. Pre- or postoperatively, the patient should be treated with amphotericin B and should be monitored with serial complement-fixation tests for *C. immitis*.

Amphotericin B causes regression and healing of disseminated foci. *C. immitis* appears to be uniformly susceptible *in vitro* to amphotericin B. Evidence suggests that it may prevent dissemination in severe primary cases. However, amphotericin B therapy carries a significant risk of death. Smale and Waechter observed two deaths associated with kidney disease from the nephrotoxicity of amphotericin B. Amphotericin B can cause up to a 40% reduction in glomerular filtration rate. This phenomenon is dose-dependent and usually reversible. Nevertheless, the morbidity and mortality of untreated disseminated disease carries an even greater risk. By gradual escalation of dosage and by careful monitoring of renal function, the adverse nephrotoxic effect of drug therapy can be markedly reduced. The effectiveness of therapy can often be measured by a decreasing complement-fixing antibody titer. The decrease is usually preceded by improvement both in the patient's clinical condition and in the changes in chest X-rays. Because of the narrow therapeutic index, systemic therapy with amphotericin B should be carried out only by skilled clinicians with prior experience and in a carefully controlled environment. The impact of amphotericin B on the developing fetus has not been fully evaluated to date.

The severity of disease and specific trimester of pregnancy may influence the choice of therapy. Nondisseminated disease occurring before the third trimester has been handled using ketoconazole, fluconazole, or miconazole.

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Mycobacterium tuberculosis and *M. bovis*

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The tubercle bacilli of the genus *Mycobacterium* are thin, straight rods measuring approximately 0.4 μm×3 μm. They are characterized by their acid-fast staining, which is contingent on the fact that, once stained by basic dyes, they cannot be decolorized by alcohol. The mycobacteria are obligatory aerobes. In contrast to most bacteria, their replicating cycle is of the order of 17–24 hours. The tubercle bacilli are relatively resistant to desiccation and may survive for long periods in dry sputum.

The bacilli produce no endotoxin. Their gross and microscopic lesions represent the summation of the proliferation of mycobacteria and the cellular reaction of the host. The initial reaction of the human host to either *Mycobacterium tuberculosis* or *M. bovis* is characterized by a polymorphonuclear neutrophilic inflammatory exudate. The polymorphonuclear neutrophils are transient and are replaced within 48 hours by monocytes and lymphocytes. Prior to the development of resistance and hypersensitivity by the host, the prime sites of tubercle replication become intracellular within monocytes and reticuloendothelial (RE) cells.

The advent of cellular immunity markedly influences the ability of the tubercle bacillus to replicate at these intracellular sites. The lesions undergo precipitous change. The intracellular destruction of the bacilli is enhanced, and caseation necrosis within fixed tissue tends to be the rule. Rechallenge with exogenous *M. tuberculosis* or reactivation of endogenous infections in an individual in whom immunity has developed results in a markedly different lesion. Rather than being exudative, the lesion elicits a proliferative granulomatous response, which in its most classic form is characterized by centrally located caseation necrosis surrounded by concentric layers of epithelial and giant cells, and finally a peripheral zone of lymphocytes, monocytes, and fibroblasts.

The portal of infection determines the mechanism by which the female genital tract is involved. Tuberculosis is primarily an infection of the respiratory tract. Female genital tract involvement can develop from a pulmonary nidus of infection or by hematogenous dissemination of organisms and their subsequent localization within the fallopian tube. When the gastrointestinal tract is the portal of infection, involvement of the ileocecal region permits lymphatic spread—primarily to the right fallopian tube.

Dissemination of disease from the fallopian tube occurs by continuous spread to potentially involve the ovary and retrograde into the uterus. Uterine extension involves primarily the endometrium with at maximum a 20% incidence of myometrial involvement. The involvement of the ovary is usually in the form of a perioophoritis. In some instances the hilus of the ovary is invaded by direct hematogenous spread. The cervix can be involved either by extension from the endometrium or as part of the hematogenous infection.

Tuberculosis of the vagina and the vulva is extremely uncommon. This type of involvement is more common in a woman with tuberculosis of another organ who excretes tubercle bacilli in her stool, urine or sputum. When in contact with the external genitalia, these secretions may result in tuberculosis of the vulva or vagina (particularly if the epithelium has been broken or damaged).

Tuberculous peritonitis is a variant on genital tract tuberculosis. Disease occurs as a consequence of an initial miliary dissemination during the primary bacillemia or secondarily during reactivation of extrapulmonary disease. Co-existence of fallopian tube/uterine disease and tuberculous peritonitis can and does coexist in up to 50% of the cases. The female genital tract may become infected with either *M. tuberculosis* (human) or *M. bovis* (bovine) strains. Although it is a rare cause of genital tuberculosis in the United States, bovine tuberculosis is not an uncommon etiologic agent of genital tuberculosis in underdeveloped countries lacking facilities for pasteurization of milk. It is probable that some of the photochromogens, such as *M. kansasii*, may eventually be shown to be pathogens of the female genital tract. Irrespective of whether human or bovine strains of *Mycobacterium* are involved, both are pathogenic for man.

FEMALE GENITAL TRACT INVOLVEMENT

Morgagni, in the mid-eighteenth century, was probably the first investigator to describe genital tuberculosis. In modern society, genital tuberculosis is almost invariably the result of seeding of the pelvic organs during tuberculous bacillemia from an extragenital focus. Involvement of the female genital tract is usually insidious and manifested late in the course of infection. Symptoms referable to the genital tract do not tend to appear immediately following colonization. An interim of 1–10 years may elapse between actual seeding and clinical manifestations. Once the disease is established, it tends to pursue a slow, indolent course. For reasons yet to be explained, the nearer a female is to menarche at the time of primary infection, the greater the likelihood of genital involvement.

Primary pulmonary infection is the consequence of the inhalation of tubercle bacilli. Because of aerosol transmission, the initial sites of infection are the lower lobes and in particular the right lower lobe. The initial host response is an acute exudative lesion. The bacilli ultimately disseminate through the lymphatics to the regional nodes. With the advent of both cellular and humoral immunity, the exudative lesion at the portal of infection (whether lung or intestines) resolves. Lymph nodes undergo caseation necrosis and possible dystrophic calcification at a later date. Calcification in tuberculous foci indicates that necrosis has previously taken place. Dystrophic calcification is not evidence of healing. The combination of primary tissue lesion (whether in lung or intestines) and involved regional nodes constitutes the Ghon complex.

A certain number of organisms, having once attained access to the intravascular compartment via the efferent lymphatics and thoracic duct, may, by hematogenous dissemination, be distributed to multiple organ systems. These organisms are responsible for the ‘Simon’s foci’ in the apical and/or posterior segments (or their equivalents) and possible deposition in the fallopian tubes. Thus, infection of the female genital tract may be caused by either acute or subacute hematogenous dissemination in an individual with active pulmonary tuberculosis. These foci can cause endogenous infection at a later date,

although in most cases they become quiescent after the development of tuberculin hypersensitivity and are of no further clinical significance.

The external portions of the perineum or vulva may on rare occasions be primary sites of infection. In these instances, genital tract involvement is via direct inoculation of infectious material. The pathogenesis is analogous to that of cutaneous tuberculosis at non-genital sites. External genital tract infection results in superficial ulcers which may have an associated development of sinus tracts. Even partial healing is characterized by fibrosis and scar formation.

CLINICAL PRESENTATIONS

In the developed countries, the clinical presentation of genital tract tuberculosis is altered. Disease is being diagnosed in an older age group which not infrequently may be perimenopausal. The most common presentation in this group is menstrual irregularity. In developing countries the principal manifestations are abdominal pain and infertility. When menstrual disturbances occur, primary amenorrhea is the most common presentation. Disease occurs primarily between the ages of 20 to 40 years of age.

Infertility

Infertility is the most common presenting complaint. Its incidence within a given population depends directly on the prevalence of extra-genital tuberculosis and ranges from 2–5% of all cases of infertility. In most cases there are no concomitant physical findings that provide a clue to the possible relationship between presenting complaint and etiology. The Mantoux intradermal skin test should be a standard part of every clinical examination for infertility. A positive reaction should alert the physician to the possibility of genital tuberculosis and argues for a culture and histologic analysis of the endometrium. A high index of suspicion when a patient is being evaluated for infertility, particularly if she is a recent immigrant from the ‘third world’, or is the prime prerequisite for diagnosing the incipient stages of genital infection or disease. Menstrual irregularities and/or dysmenorrhea may be secondary to endometrial involvement. Derangement of the menses is not an uncommon clinical manifestation in women with genital tuberculosis. Although secondary amenorrhea or oligomenorrhea is uncommon, the menstrual pattern is unpredictable. Early in the infection, an increase in menstrual flow or irregular bleeding between menses may occur. Primary amenorrhea and postmenopausal bleeding have been observed in patients with tuberculous endometritis.

Pain

About 35% of women with genital tuberculosis complain of chronic lower abdominal pain, with an incidence roughly proportional to the number of women with abnormal physical findings on pelvic examination. It is not uncommon to elicit a history of recent appendectomy or actual laparotomy performed for chronic discomfort. Pelvic pain associated with inflammatory masses that does not improve with conventional therapy should raise the suspicion of genital tuberculosis.

Ascites

A common clinical presentation is ascites secondary to peritoneal tuberculosis (Figure 59.1). The development of ascites presents a real diagnostic challenge, particularly when the patient is past the age of 20. In adolescent girls, the origin of ascitic abdominal swelling is frequently tuberculous. The swelling is often accompanied by pain and low-grade fever. Peripheral edema, which is characteristic of cardiovascular-related ascites, is not present with tuberculous peritonitis and ascites unless there is concomitant gastrointestinal involvement and resultant protein depletion.

The diagnosis of peritoneal tuberculosis can rarely be made on Ziehl-Neelsen staining of centrifuged sediment from ascitic fluid. In approximately 50% of patients, the organism can be isolated by appropriate cultures. With peritoneoscopy and biopsy, the probability of establishing the diagnosis approaches 85%; with laparotomy, 100%. Characteristic of tuberculous ascites is its failure to recur following laparotomy. Analysis of the ascitic fluid may suggest that one is dealing with an exudate rather than a transudate. Protein content greater than 3.5 g/100 ml or specific gravity greater than 1.015 are characteristic of the former. However, the specific gravity is in part a function of the density of peritoneal lesions and may vary considerably. A specific gravity less than 1.010 probably excludes tuberculosis from consideration. In general, there is a better correlation between protein content and causative factors than between specific gravity and etiology.

Physical signs of genital tuberculosis

Female genital tract organs infected with *M. tuberculosis* may appear entirely normal on physical examination. In only about 50% of the cases does bimanual examination reveal physical findings indicative of pelvic disease, such as enlargement or fixation of appendages, pyosalpinx, or abdominal swelling secondary to tuberculous peritonitis. Extensive adhesions in pelvic tuberculosis reflect the previous occurrence of tuberculous peritonitis. Even at laparotomy, unless tuberculous peritonitis with serosal seeding of the peritoneum or pyosalpinx is present, the diagnosis may not be evident on gross examination of the fallopian tubes and may be contingent on tubal biopsy or culture.

The fallopian tubes, like their embryologic male homologue, the epididymis, are the initial sites of pelvic

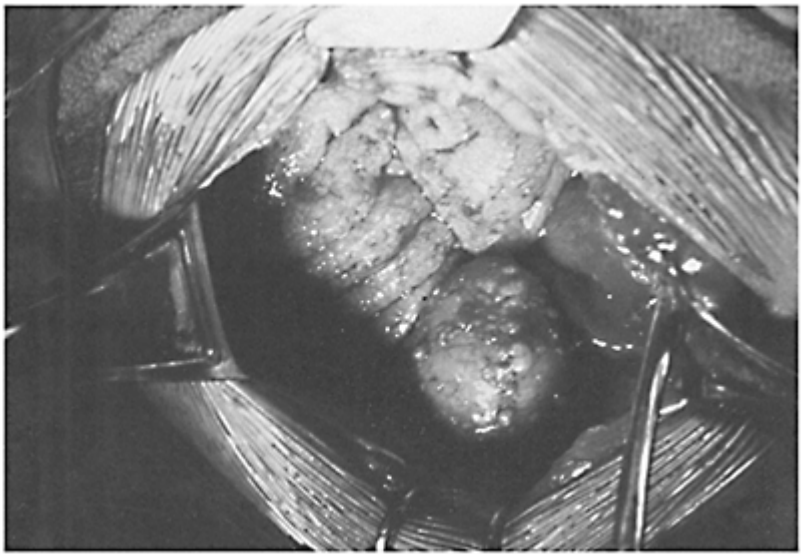

Figure 59.1 Coalescing miliary lesions, at laparotomy, involving the serosa, omentum, and peritoneal surfaces in a 16-year-old nulligravida who presented with ascites

involvement following hematogenous dissemination of the bacilli, with the distal portions appearing to be infected first. Infection then takes a more central path, with the uterus being ultimately involved. In a significant number of cases, endometrial biopsy fails to reveal the bacilli or histologic evidence of infection, even though the disease process is entrenched in the fallopian tubes. In approximately one-quarter of the cases of genital tuberculosis, the fallopian tubes are patent. Within the endometrium and the interstitium of the fallopian tubes, the tissue response to *M. tuberculosis* is that of epithelioid cell granulomas with or without scattered Langhans' giant cells (Figure 59.2). Fibrosis marginal to the granuloma is usually present, as is lymphocytic infiltration. Caseation necrosis is rare and tends to be a late feature.

The endometrial glands frequently exhibit underdeveloped secretory patterns or a pattern of glandular hyperplasia. Epithelial hyperplasia may be so striking, with respect to fallopian tube lesions, as to be misinterpreted as a coexistent well-differentiated adenocarcinoma. The presence of numerous plasma cells, as well as of lymphocytes, within the endometrial stroma is indicative of secondary infection.

TUBERCULOSIS OF THE BREAST

Tuberculous mastitis usually presents in the third decade of life. The patients usually present with a unilateral painful breast mass arising over weeks or a painless, non-friable lump of short duration. The latter presentation is usually with lymphadenopathy. Occasionally a draining sinus is presented. Rarely is tuberculous etiology postulated. The pre-biopsy diagnoses are usually equally divided between breast abscess and carcinoma. The diagnosis of tuberculosis was based on the histopathological demonstration of tubercles, caseation and a granulomatous inflammation with acidfast bacilli. The differential diagnosis includes duct ectasia, a foreign-body giant-cell reaction with fat necrosis, foreign body abscess, granulomatous mastitis, fungal mastitis, sarcoidosis and a syphilitic gumma. The diagnosis

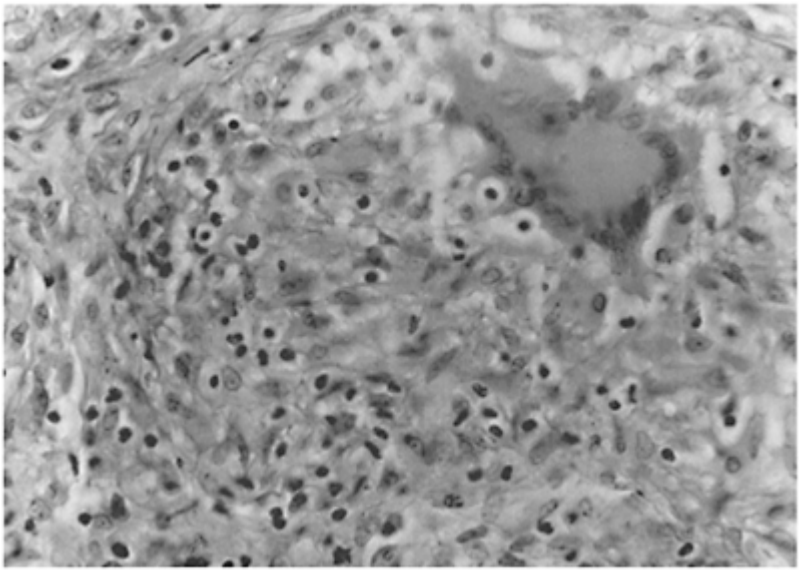

Figure 59.2 Granuloma associated with *M. tuberculosis* demonstrating epithelioid cells and a single Langhans' giant cell associated with *M. tuberculosis*

is usually made by cultures of breast aspirate or by histological analysis of the biopsy sample. Treatment involves complete surgical excision of the lesion and at least six months of postoperative anti-tuberculous chemotherapy.

DIAGNOSIS

PPD intradermal skin test (Mantoux)

The diagnosis of infection due to *M. tuberculosis* is contingent upon the demonstration of a positive purified protein derivative (PPD) tuberculin skin test. Based on the sensitivity and specificity of the PPD skin test, three different cut-points have been recommended for defining a positive tuberculin reaction.

When intermediate strength PPD in a dose of 0.1 ml (5 tuberculin units [TU]) is injected into the dermis over the forearm of a tuberculous patient, a positive tuberculin reaction, characterized by an area of induration more than 10 mm in diameter, develops within 48 hours. Reactions less than 5 mm in diameter are read as negative and those inbetween 5 mm and 10 m as indeterminant. For persons who are at the highest risk for developing active disease if they become infected by *M. tuberculosis* a 5 mm or greater induration is considered positive. This group includes persons with HIV infection, persons receiving immunosuppressive therapy, persons who have had close contact with an active case, and persons who have chest radiographs consistent with previous tuberculosis (Table 59.1).

A positive reaction indicates infection but does not necessarily correlate with active disease at the time of testing.

About 10% of patients with bacteriologically confirmed tuberculosis may fail to respond to 5 TU of PPD as well as to several purified protein products containing polysorbate 80 (Tween 80). Such individuals tend to react to second-strength PPD. A tuberculin test should not sensitize a non-infected person, but it can stimulate or enhance remotely established hypersensitivity. To circumvent the problem of the ‘booster effect’, retesting should be done one week later. If the second test is positive, it is probably due to magnification of subclinical hypersensitivity to prior infection more than to new infection. Patients with miliary tuberculosis or overwhelming pulmonary tuberculosis may exhibit anergy.

Table 59.1 Criteria for a positive tuberculin test

A reaction of ≥15 mm is classified as positive in all individuals
A reaction of ≥10 mm is classified as positive in the following groups:
• Foreign-born individuals from high prevalence areas, eg. Asia
• Intravenous drug users
• Medically underserved—low income populations
• Residents of long-term care facilities
• Individuals with medical risk factors e.g. chronic renal disease, corticosteroids, lymphomas, leukemias, silicosis, gastrectomy, jejunoileal bypass, diabetes mellitus, weight loss of 10% of ideal body weight
A reaction of ≥5 mm is classified as positive in the following groups:

- HIV positive individuals
- Individuals receiving immunosuppressive therapy
- Individuals with recent contact with active case of tuberculosis
- Individuals with chest X-ray consistent with old healed TBC

Interpretation of PPD in HIV-infected persons is as follows:

- 50% of HIV-positive individuals are anergic. A non-reactive PPD does not preclude the presence of *M. tuberculosis*
- Positive skin test is positive if the induration is 5 mm in diameter

The value of the skin test in infertility cases is to increase the index of suspicion and identify that population in whom culture techniques should be applied. Otherwise, its real value lies not in identifying those individuals with previous infection but in excluding tuberculosis from the differential diagnosis. A nonreactive skin test does not exclude infection in cases of tuberculous peritonitis or miliary tuberculosis.

Tuberculin reactivity caused by bacillus Calmette-Guerin (BCG) vaccination generally wanes with time. It can be boosted by the tuberculin skin test. While no reliable method exists to distinguish tuberculin reactivity caused by vaccination with BCG from those caused by natural infection, reactions of 20 mm or greater of induration are not likely to be caused by BCG.

Histology and microbiological culturing

The diagnosis may be established on the basis of the histopathologic features of a premenstrual endometrial biopsy or curettage fragments. Classically, one-half of endometrial fragments are sent for culture and the other half for histologic examination. The diagnosis is generally established by the presence of characteristic granulomas in the material analyzed. Failure to demonstrate the acid-fast bacilli by the Ziehl-Neelsen technique does not invalidate the diagnosis except in the absence of evidence of delayed hypersensitivity (i.e. a negative PPD).

Occasionally, histologic examination of the endometrial curettement alone does not reveal the disease process (due to sampling errors or to non-involvement of the endometrium when the fallopian tubes are the prime sites of infection). Bacteriologic examination is important and should be done. Menstrual blood collected in a Tassette cup provides additional material for culture. At some future date, the current rapid culture techniques such as radiametric and biphasic methods and microcolony morphology will give way to DNA probes and high performance liquid chromatography.

Hysterosalpingograms may reveal closed tubes with a ‘tobacco-pouch’ deformity of the ampullary end or a rigid ‘pipe-stem’ pattern (Figure 59.3). In contrast to the morphologic changes in chronic salpingitis, the fimbriae are uninvolved. Some of the infected tubes demonstrate multiple fistulas.

Targeted scanning of the uterus and fallopian tubes is possible with high-resolution transvaginal sonography.

Once the diagnosis of genital tuberculosis is established, the patient's evaluation should include:

(1) chest X-ray;
(2) three sputum collections for tubercle bacilli;
(3) IV pyelogram; and
(4) three urine cultures for tubercle bacilli.

While renal involvement will not alter therapy, these cultures are important as an additional source for culture material to assure a bacteriologic diagnosis and specimens for sensitivity testing. Ten percent of women with genital involvement have renal tuberculosis, and vice versa. All positive cultures need to be tested against a primary susceptibility test panel of five drugs which

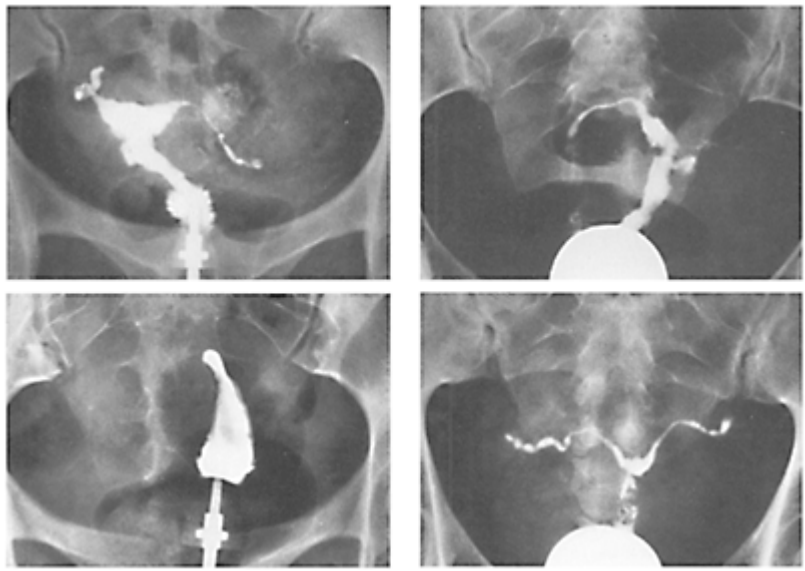

Figure 59.3 Patterns of tubal disease due to *M. tuberculosis* as demonstrated by hysterosalpingograms. Irregularity of the endometrial cavity (A). Rigid 'pipe-stem' pattern (B). 'Tobacco-pouch' deformity (C). Beading within the tubal lumens (D). (Courtesy of Thomas Klein, MD, Bethesda, MD)

include isoniazid (INH), pyrazinamide, ethambutol, streptomycin and rifampin.

Targeted tuberculin testing of populations at risk for acquisition of infection or its progression to disease is a strategic component of tuberculosis control.

Treatment of latent tuberculosis

A number of regimens have been recommended for the treatment of latent tuberculosis. The INH daily regimen for nine months is recommended. Before beginning treatment for latent tuberculosis, active disease should be ruled out by history, physical examination, chest radiography, and when indicated bacteriologic studies.

For pregnant, HIV-negative women, INH given daily or twice a week for 6 or 9 months is recommended. For women at risk for progression to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even in the first trimester. For women whose risk for active tuberculosis is lower, waiting until after delivery or at least the first trimester should be evaluated on an individual basis.

Twice-weekly treatment with rifampin and pyrazinamide for 2 or 3 months may be considered when isoniazid cannot be given. To avert drug resistance, it is recommended that this regimen be given as five observed and two self-administered doses each week. In situations such as HIV-infected persons receiving protease inhibitors, in which rifampin cannot be used, rifabutin may be substituted.

Once a patient has been identified, they should receive appropriate follow-up surveillance at least monthly. Baseline evaluation of pregnant women, women with HIV and women within three months of delivery, and women with hepatitis B, hepatitis C or alcoholic hepatitis include evaluation of measurements of serum aspartate aminotransferase or alanine aminotransferase and bilirubin.

CONGENITAL TUBERCULOSIS

Congenital tuberculosis is a rare but well-defined entity. With the notable exception of miliary tuberculosis, there is no predictable correlation between maternal disease and the probability of infection of the conceptus. Fetal infection may take place when the maternal lesions are minimal. This lack of correlation reflects the fact that tuberculous bacillemia may occur at any time during activity of an existing focus of infection. Fetal infection results primarily as a consequence of maternal bacillemia. If a thrombus containing mycobacteria forms in the intervillous spaces and if the inflammatory process proliferates so as to involve the adjacent placental area, embolization of infectious material to the fetus may occur.

Placental involvement attending maternal hematogenous bacillemia occurs far more frequently than infection of the fetus. Limitation of infection to the placenta may be in part a function of maternal immunity. Thrombosis of fetal vessels draining a nidus of infection is more likely to occur when placental involvement is the consequence of chronic hematogenous dissemination from a mother with longstanding disease rather than from one with miliary tuberculosis. When placental involvement is grossly discernible, examination of the umbilical cord may occasionally reveal multiple tuberculous granulomas around the umbilical vein.

With congenital disease the primary complex develops in the liver or regional lymph nodes, or both. In contrast to adult tuberculosis, in which hepatic involvement is usually limited to small granulomas in the portal area, extensive and progressive destruction is observed in the fetal liver. This preferential growth within hepatic tissue *in utero* may

reflect the dependence of *M. tuberculosis* on an oxygen-rich environment which in fetal life is supplied by the umbilical vein. Although hepatic involvement is probably caused by secondary hematogenous spread of tubercle bacilli from a placental focus, extensive nodal involvement of the porta hepatis can conceivably be the result of lymphatic spread from an infected placental focus to the regional lymph nodes.

A second mechanism for congenital infection occurs in women with tuberculous endometritis. The majority of such women are sterile owing to prior fallopian tube involvement; this circumstance accounts for the rarity of congenital tuberculosis based on this mode of dissemination. By direct extension the tuberculous process may either involve the placenta—from which there is subsequent dissemination to the fetus—or erode directly into the amniotic fluid with subsequent fetal aspiration of infected material. In those cases in which this latter mode of transmission appears to be reasonably documented, the infants quickly succumb to tuberculous bronchopneumonia. When the degree of aspiration is relatively small, a successful response to antituberculosis therapy may be achieved.

At necropsy infants with congenital tuberculosis usually exhibit macromiliary lesions of spleen, liver, and lungs. Microscopic examination reveals tuberculous granulomas with characteristic epithelial, mononuclear, and Langhans' giant cells and caseation necrosis. Occasionally, the lesions show only caseation necrosis with very little reaction. When the lesion has extended to a free surface, the response is predominantly one of mononuclear cells. This is most pronounced in tuberculous pneumonia in which endotracheal spread has occurred. In 'fixed tissue' (intra-alveolar walls, spleen, liver), the more characteristic epithelioid response is observed. Both reactions may be seen in the same infant and are primarily related to the site of the lesion.

In aspiration-type congenital tuberculosis, the lungs are the sole organ of involvement. The disease process is confined to the alveoli, with an intra-alveolar exudate composed predominantly of macrophage and alveolar lining cells with an accompanying alveolitis.

Fetal tuberculous bacillemia results in dissemination of the organisms primarily to the liver, bone marrow, spleen, lung, and renal cortex. Less frequent sites of involvement include brain, skin, and adrenal glands. The distribution of the lesions parallels that of the reticuloendothelial cells and reflects the fact that *M. tuberculosis* behaves like particulate matter in the intravascular compartment.

Clinicopathologic correlations

Although a few cases of congenital tuberculosis have been documented shortly after birth, in most instances the symptoms evolve insidiously during the first months of life. The infants refuse to eat, with ensuing weight loss. Splenomegaly and eventually hepatosplenomegaly develop. Obstructive jaundice may develop as a result either of extensive hepatic involvement or, more frequently, of impingement on the biliary system by enlarged nodes in the porta hepatis. In more than half of the cases reported, the infants died within 3 to 4 weeks after the first sign of illness. Others, primarily those with pulmonary aspiration tuberculosis or extensive miliary dissemination, developed respiratory distress. These infants died early with tuberculous bronchopneumonia. Oddly enough, tuberculous meningitis is not common in cases of congenital involvement. The

short interim between diagnosis and death stresses the necessity for prompt diagnosis and institution of therapy, despite an anticipated high mortality.

Diagnosis

Congenital tuberculosis essentially requires that certain criteria be met:

(1) the primary tuberculous complex must be present in the liver;
(2) extrauterine acquisition of infection must be definitely excluded; or
(3) the tuberculous lesions must be present at birth.

The diagnosis of congenital tuberculosis should be actively sought in the progeny born to mothers with active cavitary, pelvic, or miliary tuberculosis who are not receiving therapy. Placental examination is of limited value in the identification of congenital tuberculosis. Tuberculous involvement of the placenta is a more frequent phenomenon than congenital infection. Negative histologic examination of the placenta does not exclude the possibility of hematogenous dissemination. The likelihood that congenital tuberculosis will occur in any particular case cannot be predicted either by consideration of the mother's lesions or by the presence of foci of infection in the placenta.

Management of neonates born to tuberculous mothers

Infants born to mothers with active tuberculosis represent a real challenge in clinical therapeutic management. If disease has been established *in utero,* there is the necessity of instituting immediate therapy if the baby is to survive. Equally important is the opportunity to institute prophylaxis which may guard the neonate against subsequent acquisition of infection.

The infants of mothers being treated for active tuberculosis whose cultures are negative for *M. tuberculosis* merely need to be tuberculin-tested between the second and fourth week of life with 5 TU 0.1 ml (intermediate-strength) PPD and thereafter at 2-month intervals during the first year of life. Infants born to mothers with active tuberculosis and sputum that is positive for *M. tuberculosis* 'should be treated with INH for two to three months or at least until the mother is smear and culture negative and known to be complying with therapy. If after three months of therapy the mother has a negative sputum smear and the infant is tuberculin negative and has a normal chest X-ray, INH may be stopped'. When the maternal disease is either miliary tuberculosis or tuberculous meningitis, owing to the 30% risk of congenital infection, the infant is immediately placed on INH therapy, 10 mg/kg/day, after baseline gastric and cerebrospinal fluid cultures, hepatic transaminase determinations, chest X-rays, and tuberculin skin tests have been obtained. If the tuberculin test is positive or congenital infection is documented by

Table 59.2 Potential fetal adverse drug reactions due to antituberculous therapy

Drug	***Potential adverse effects on fetus/neonate***
Cycloserine (Seromycin®)	Safety not established

Ethambutol (Myambutol®)	Not known—teratogenic in animals
Ethionamide (Treacator-SC®)	Teratogenic in animals
Isoniazid (INH and others®)	Embryotoxic in animals
Pyrazinamide	Unknown
Rifampin (Rifadin®; Rimactane®)	Teratogenic in animals

isolation of the tubercle bacillus, the INH dosage can be increased to 20 mg/kg/day and rifampin 10–20 mg/kg po each day for nine months. Maternal antibacterial therapy during pregnancy may have an adverse fetal effect (Table 59.2). Ethionamide and rifampin are best avoided during pregnancy when possible.

If the neonate exhibits any evidence of an infectious process, antituberculosis therapy should be instituted despite a negative PPD test. Not infrequently, an infant with extensive disease may exhibit a transient anergy; however, failure of the PPD test to become positive after 3 to 4 weeks of therapy would be evidence against the diagnosis of congenital tuberculosis.

It is not always possible to obtain the organism for determination of sensitivities to antituberculous chemotherapeutic drugs. Attempts can be directed toward isolating the organism from the maternal host as an acceptable alternative.

Therapy

Infants born to mothers with active pulmonary tuberculosis require the same baseline studies. The critical point in their management is to determine whether the tuberculin test is positive or negative. The tuberculin test being positive, the infant is given the therapeutic regimen for congenital tuberculosis. The tuberculin tests obtained in the second and fourth weeks of life being negative, three methods of management are available:

(1) The child may receive INH for six months to one year and be tuberculin tested every 2 months during chemoprophylaxis. The effectiveness of INH prophylaxis is dependent upon patient compliance. Whenever the tuberculin test becomes positive or culture evidence of infection with *M. tuberculosis* is obtained, the child is treated with the full therapeutic regimen.
(2) The second method is cultural, roentgenographic, and tuberculin surveillance for one year. This requires adequate health facilities and full parental cooperation. In addition, the mother's sputum should be culture-negative and the infant's chest X-ray normal, with no exposure of the infant to active tuberculosis in the immediate family.
(3) The third method of management is BCG vaccination, prior to which the patient's roentgenogram should be normal and the tuberculin test negative.

BCG is advocated in those cases involving poor or indifferent parental motivation, a socioeconomic impediment to surveillance or therapy, or inadequate health facilities. Kendig made a follow-up study of 105 infants born to tuberculous mothers. Of the 30 who received BCG vaccine, none contracted tuberculosis. Of the 75 non-vaccinated infants, 38 became infected. In this study, the known inadequacy of an imperfectly

followed regimen of culture surveillance or chemoprophylaxis combined to make BCG vaccination the method of choice for non-compliant individuals. Neonates born to mothers with current active tuberculosis should be treated with INH for two to three months or at least until the mother is smear and culture negative and known to be compliant with therapy. If the infant's tuberculin reaction is significant at three months, a posterior-anterior and lateral radiograph are required.

PREVENTIVE THERAPY OF TUBERCULOUS INFECTION

A single drug, INH, is used for preventive therapy in a dose of 300 mg per day for adults and 10 mg per kg body weight per day, not to exceed 300 mg per day for children, to be administered in a daily single dose over a period of six to twelve months. INH is inexpensive, administered orally, and easy to take. Mild hepatic dysfunction, evidenced by elevation of serum aminotransferase (transaminase) activity, occurs in 10–20% of persons taking INH. This abnormality usually occurs in the first four to six months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. On occasion, progressive liver damage occurs and presents symptoms; the drug should be discontinued immediately in these cases. The frequency of progressive liver damage increases with age. It is rare in individuals under age 20. The observed frequency in other age groups is as follows: ages 20–34, up to 0.3%; ages 35–49, up to 1.2%; 50 years and more, up to 2.3%. Pregnant and postpartum Hispanic women may have a two-fold increase in morbidity.

Persons for whom preventive therapy is recommended

Priorities must be set for preventive therapy, taking into consideration not only the risk of developing tuberculosis compared with the risk of INH toxicity, but also the ease in identifying and supervising persons for whom preventive therapy is indicated, and their likelihood of infecting others. The following groups are listed in order of priority:

(1) **Household members and other close associates.** Household members and other close associates of patients with newly discovered tuberculous disease are at high risk of being recently infected and of developing disease. The risk is approximately 2.5% for the first year. However, the risk is approximately 5.0% for those already infected (tuberculin positive) at the time of the initial examination. Contacts of patients should be examined and those diagnosed as having tuberculous disease should be treated with multiple drug therapy. All other contacts with Mantoux tuberculin skin test readings of 5 mm or more should receive preventive therapy, since in this group such reactions are likely to be due to infection with *M. tuberculosis*.

(2) **Positive tuberculin skin test reactor with abnormal chest roentgenogram.** Persons with past tuberculous disease not previously treated by adequate chemotherapy and tuberculin skin test reactors with roentgenographic findings consistent with non-progressive tuberculous disease should receive preventive therapy The rate of reactivation in such groups, if untreated, has been observed to range between 1.0% and 4.5% per year.

(3) **Newly infected persons.** The risk of developing tuberculous disease for the newly infected is about 5.0% during the first year after infection. Because this excess risk is concentrated in the first year or so, the term newly infected persons should be applied only to those who have had a tuberculin skin test conversion within the past 2 years.

Preventive therapy is mandatory for positive reactors through age 6 years and highly recommended to age 35 years, unless there are contraindications to the use of INH, as listed below.

Among positive tuberculin reactors aged 35 years and more, the risk of hepatitis precludes the routine use of preventive therapy unless an additional risk factor (such as contacts or converters) is present. Thus, persons 35 and more with normal chest roentgenograms and no other risk factors are not, as a group, recommended for preventive therapy. Rather, they should be considered for preventive therapy on an individual basis in situations where there is a likelihood of serious consequences to contacts who may become infected.

Screening procedures

Before INH for preventive therapy is started, the following screening procedures should be carried out:

(1) Rule out bacteriologically positive or progressive tuberculous disease. Every person who is a positive reactor should have a chest roentgenogram taken. If there are findings consistent with pulmonary tuberculous disease, further studies-medical evaluation, bacteriologic examinations, and comparison with previous roentgenographic findings-should be made to rule out progressive disease. This is because persons with progressive or bacteriologically confirmed tuberculous disease require more intensive chemotherapy than is given for preventive therapy
(2) Question for a history of INH administration to exclude those who have had an adequate course of the drug.
(3) Ascertain the presence of contraindications to the administration of INH for preventive therapy, which are:

   (a) previous INH-associated hepatic injury;
   (b) severe adverse reactions to INH, such as drug fever, chills, and arthritis; and
   (c) acute liver disease of any etiology.

(4) Identify patients for whom preventive therapy is not contraindicated but in whom special attention is indicated by the following:

   (a) Concurrent use of any other medication on a long-term basis (in view of possible drug interactions).
   (b) Use of diphenylhydantoin, the dosage of which may need to be reduced to avoid diphenylhydantoin toxicity. This is because in some individuals INH may decrease the excretion of diphenylhydantoin or may enhance its effect.
   (c) Daily use of alcohol, which may be associated with higher incidence of INH hepatitis.

(d) Previously discontinued INH because of possible but not definitely related side-effects (e.g. headaches, dizziness, nausea, etc.). Possibility of current chronic liver disease.

Isoniazid toxicity

Isoniazid toxicity usually manifests with biochemical evidence of hepatic dysfunction. Approximately 10–20% of patients taking the drug will have some elevation of transaminase activity. This abnormality usually occurs in the first four to six months of treatment, but can occur at any time during therapy. In most instances, the enzymatic abnormalities return to normal despite continued drug therapy Unless there is progressive evidence of hepatic decompensation, discontinuation of the medication is not necessary

Monitoring individuals for INH toxicity

Individuals receiving preventive therapy should be questioned carefully at monthly intervals for the following:

(1) Symptoms consistent with those of liver damage or other toxic effects; that is, unexplained anorexia, nausea, or vomiting of greater than 3 days' duration, fatigue or weakness of greater than 3 days' duration, persistent paresthesia of the hands and feet;
(2) Signs consistent with those of liver damage or other toxic effects; that is, persistent dark urine, icterus, rash, elevated temperature of greater than 3 days' duration without explanation.

Monitoring by routine laboratory tests (e.g. serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase, serum bilirubin, and alkaline phosphatase) is not useful in predicting hepatic disease in INH recipients and therefore is not recommended. However, in evaluating signs and symptoms such tests are mandatory Preventive therapy should be reinstituted only if biochemical studies are normal and signs and symptoms are absent.

In some instances, an SGOT may be obtained for some reason other than the presence of signs or symptoms. If the result of this test does not exceed three times normal and no signs or symptoms have developed, the drug may be continued with caution and careful continued observation. If the level exceeds three times normal, the decision to continue INH should be based on careful evaluation for liver damage and the reason for preventive therapy.

MANAGEMENT OF NEWLY ACQUIRED TUBERCULIN REACTIVITY IN PREGNANCY

If pre-existing disease is treated prior to gestation, pregnancy does not appear to reactivate or aggravate it. The problem occurs when a gravida becomes tuberculin-positive during pregnancy. All four of the first-line drugs (INH, ethambutol, rifampin, and streptomycin) have apparent reasonable margins of safety when used during pregnancy. The American Thoracic Society, American Lung Association, and the Centers

for Disease Control identify the relative safety of INH for the fetus. It is their recommendation to prescribe only therapeutically necessary medication during pregnancy. This position is not universally accepted.

Pregnancy is not without its effect on disease due to *M. tuberculosis*. Women in whom tuberculosis is discovered during pregnancy tend to fare much worse than do women in whom the diagnosis is made prior to conception. When disease occurs in the third trimester or the immediate postpartum period, fulminating disease (e.g. miliary dissemination or meningitis) is more characteristic than it is in the non-pregnant female or the gravida in the first trimester. These observations tend to confirm the concept that late in gestation a significant depression of cell-mediated immunity occurs. Responsiveness to lymphocytoblast mitogens as measured by blast transformation or delayed cutaneous hypersensitivity is markedly depressed in the third trimester.

THERAPY

Risk of developing tuberculosis

The probability of developing tuberculosis can be crudely approximated by using two factors: tuberculin reactivity and roentgenographic evaluation of the chest. If a woman has a positive PPD test and a normal chest X-ray, the risk of tuberculosis relapse is between 0.03 and 0.08% per year. If the chest X-ray film is abnormal, the incidence of relapse becomes 0.8–2% per year. In selected populations such as the Vietnamese and Haitian refugees, the risk of relapse per year can be as high as 6.7%.

Pulmonary tuberculosis

When primary drug resistance is unlikely, the combination of INH and ethambutol (EMB) for a period of 18–24 months has been standard therapy for mild or moderately severe disease (Table 59.3). Triple therapy with the addition of streptomycin (STM) has been used for advanced cavitary disease. INH, 300 mg, EMB, 15–18 mg/kg for outpatients and 25 mg/kg for inpatients, and STM, are used for the first three months, or until sputum is negative for advanced cavitary disease. After a two-month course, a twice weekly schedule of INH, 15 mg/kg, plus EMB, 50 mg/kg, or STM, 25–28 mg/kg, has been administered. This regimen can be used for intermittent therapy to ensure patient compliance.

Relatively comparable therapeutic results have been obtained with regimens containing both INH and rifampicin (RIF) over nine months. The combination of INH (300 mg) plus RIF (600 mg) given once daily by mouth on an empty stomach for nine months is now an established therapy for all forms of pulmonary and extrapulmonary disease. An alternate therapy is rifampicin, INH and pyrazinamide for two months. A variation has INH and RIF administered daily for one or two months followed by 900 mg of INH and 600 mg of RIF given twice weekly. The more recent CDC recommendations are summarized in Table 59.4.

Patients receiving INH and RIF together may develop a rapidly progressive toxic heptatis. Individuals receiving INH and especially streptomycin and RIF need to be monitored by liver function tests since minor enzymatic changes are common.

Pending sensitivity studies, EMB (15 mg/kg) or STM (1 g) is often added to the early stages of therapy. The problem of the emergent drug resistance during therapy is usually linked to prior erratic antituberculous treatment. This problem is common in immigrants from Southeast Asia.

Table 59.3 *Mycobacterium tuberculosis:* drugs commonly used in the therapy

Drug	***Dose***	***Duration***	***Side effects***
Isoniazid	(INH) 5 mg/kg/day Max. 300 mg	9 months	GI distress, hepatitis, seizures, peripheral neuritis, hypersensitivity reactions
Rifampin	(RIF) 10 mg/kg Max 600 mg	9 months	GI distress, hepatitis, headache, purpura, febrile reaction, orange secretions
Pyrazinamide* Max 2 g/day	(PZA)l5–30mg/kg Max. 4 g	8 weeks or until cultures are sensitive to INH/ RIF	Hepatitis, hyperuricemia, arthralgias, gout
Ethambutol	(ETH) 5–25 mg/kg Max. 2.5 g/day	8 weeks or until cultures are sensitive to INH/ RIF	Altered visual acuity, red-green disturbance, optic neuritis, skin rash

*To be started initially only if resistance to INH is likely or in individuals infected with HIV
(Adapted from *MMWR* 1993; 42/ No.RR-7:1)

Genital tuberculosis

The principles of chemotherapy for tuberculosis which has extended beyond the lung are the same as those for pulmonary tuberculosis. Two or more drugs, each individually effective, must be given to reduce the chance of emergence of resistant organisms; treatment must be prolonged for 18 to 24 months.

Many advanced cases will exhibit marked resolution of the abnormal physical findings under multiple drug therapy. However, surgical intervention is necessary if there is persistence or recurrence of:

(1) adnexal masses after at least six months of drug therapy;
(2) pain; or
(3) drug-resistant infection.

Surgical treatment should at minimum involve removal of both tubes; in some European clinics this is standard procedure. The ovaries are infected in only about 5% of the cases. Even though the ovary is extremely resistant to tuberculous involvement, for technical reasons it can seldom be preserved. The ovaries are almost invariably trapped in a mass

of scar tissue, and the best surgical resolution is bilateral salpingo-oophorectomy and hysterectomy. Because of the possibility of inducing chronic fistulas, where possible, drains should not be used.

Early detection and therapy of gravidas with active disease can probably abort or prevent the majority of cases of congenital tuberculosis. Women with active tuberculosis require therapy with two or more drugs. Isoniazid, ethambutol and rifampicin are the most commonly used antituberculous drugs in pregnancy

Although neurotoxicity has not been noted among neonates whose mothers received INH during pregnancy, maternal treatment with the drug during gestation is thought to cause retarded psychomotor activity and, in some instances, mental retardation in the progeny. This phenomenon presumably is due to interference with pyridoxine metabolism by degradation compounds from isoniazid. To counter-balance this possibility, when INH is administered during pregnancy, it is advocated that vitamin B6, 50 mg daily, be given for possible fetal as well as maternal indications.

Patients with pulmonary tuberculosis during pregnancy should be treated with INH and EMB in the prescribed dosages for 18–24 months. In cases of open cavitary tuberculosis or for advanced disease, RMP may be added.

Table 59.4 Regimen options for the initial treatment of tuberculosis (TB) in adults

TB without HIV infection			*TB with HIV infection*
Option 1	***Option 2***	***Option 3***	
Daily isoniazid, rifampin, and pyrazinamide for 8 weeks followed by 16 weeks of isoniazid and rifampin daily or 2–3 times weekly (see text)*. Ethambutol or streptomycin should be added to the initial regimen until sensitivity to isoniazid and rifampin is demonstrated. Continue treatment for at least 6 months total and 3 months beyond culture conversion. ConsultTB medical expert if patient remains smear or culture positive after 3 months.	Daily isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol for 2 weeks followed by twice weekly* administration of the same drugs for 6 weeks, and subsequently twice weekly isoniazid and rifampin for 16 weeks. ConsultTB medical expert if patient remains smear or culture positive after 3 months.	Treat with directly observed therapy 3 times weekly,* with isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin for 6 months. Consult TB medical expert if patient remains smear or culture positive after 3 months.	Options 1, 2, or 3 can be utilized, but treatment regimens must continue for a total of 9 months and at least 6 months beyond culture conversion.

*All regimens administered twice weekly or three times weekly should be monitored by directly observed therapy (*MMWR* 1992; 41/No.RR-10)

Tuberculosis in pregnancy

For pregnant women the treatment regimen must be adjusted. STM may cause congenital deafness. STM is the only licensed anti-TB drug documented to have harmful effects on

the fetus. Routine use of pyrazinamide (PZA) also is not recommended during pregnancy because the risk of teratogenicity has not been determined. In addition, since the 6-month treatment regimen cannot be used and a minimum of 9 months of therapy is recommended, the preferred initial treatment is INH, RIF, and EMB. If resistance to other drugs is likely and susceptibility to PZA also is likely, the use of PZA should be considered and the risks and benefits of the drug carefully weighed. Because the small concentrations of anti-TB drugs in breast milk do not produce toxicity in the nursing newborn, breastfeeding should not be discouraged. Further, because these drug levels are so low in breast milk, they cannot be relied upon for either prophylaxis or therapy for nursing infants.

Postmenopausal tuberculosis

In the postmenopausal woman, several additional factors influence treatment. If a curettage reveals endometrial tuberculosis and an adnexal mass is palpable, one cannot be certain whether the mass is malignant, hence surgery is indicated after a short course of chemotherapy. STM should be avoided in the elderly patient because of possible damage to both auditory and vestibular functions of the eighth nerve. Several days of continued administration, after symptoms appear, may result in irreversible damage.

For the postmenopausal woman with endometrial tuberculosis and other pelvic pathology, either uterine or adnexal, an effective regimen is INH and RIF for two months followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. INH and RIF are then continued for seven months. For the postmenopausal patient in whom no adnexal masses are found, whose medical condition precludes major surgery, or who is non-compliant, the following schedule is suggested: 30 mg INH and 600 mg RIF for one month and then 900 mg INH and 600 mg RIF twice weekly for eight months. Concomitant use of PZA can reduce the duration of therapy to six months.

Genital tract tuberculosis discovered at operation

If endometrial tuberculosis is discovered at curettage, the patient should immediately be given INH 300 mg and RIF 600 mg. EMB should be added if the possibility of resistance exists. The concurrent use of PZA can shorten the treatment time to six months. The patient should be examined at monthly intervals and, if no adnexal masses are palpable, therapy should be continued for a minimum of nine months. After six months, a curettage should be performed and repeated after one year. If no recurrence has occurred, no further therapy is necessary. A search for extragenital lesions of tuberculosis should be done at the inception of treatment.

Disease is occasionally first discovered postoperatively after removal of one or both tubes. If a total abdominal hysterectomy and bilateral salpingectomy were performed, the patient should receive INH, RIF and EMB drug therapy—INH, RIF, and EMB for two months and then INH and RIF for two months. EMB should be added if resistance is demonstrated. Thereafter, the patient should receive INH and RIF for an additional seven months. EMB cannot be substituted for RIF in the shortened course of therapy. If EMB is used with INH, the duration of postoperative therapy should be for 18 months. If only

one tube was removed, drug therapy should be started with the remaining tube removed after two months and INH and RIF continued for seven months.

TUBERCULOSIS AND HIV

Individuals with recently acquired *M. tuberculosis* infection are at relatively high risk of developing active tuberculosis; in general, 5–10% of persons develop active disease within 2 years of primary infection. Individuals who have tuberculosis infection and subsequently acquire HIV infection are more likely to progress to tuberculosis disease than those who are HIV negative. Furthermore, persons who are HIV infected and subsequently are exposed to tuberculosis are more likely to progress from infection to disease than those who are HIV negative—and they are likely to have a rapid, severe progression of illness. Approximately 10% of the 1 million persons in the United States infected with HIV are also infected with tuberculosis. The prevalence of HIV infection among patients with tuberculosis disease varies around the country but may exceed 40% in some areas.

For HIV infected persons, the higher disease attack rate and the shorter incubation period associated with newly acquired tuberculous infection and the high mortality rate associated with tuberculosis disease reinforce the rationale for the use of preventive therapy. In HIV-infected persons who become newly infected with *M. tuberculosis,* the use of drug therapy should be considered treatment of incubating or subclinical disease. A significant percentage of HIV-positive cases will be infected with multi-drug resistant strains.

MULTI-DRUG RESISTANT MYCOBACTERIUM TUBERCULOSIS (MDR-TB)

The most potent factor that increases the probability that a person infected with *M. tuberculosis* will develop active tuberculosis is coinfection with HIV. The next most predictive factor for MDR-TB in newly infected individuals is exposure to a source with multi-drug resistant strains.

Resistance emerges from chromosomal mutations in specific genes. MDR-TB does not have any plasmids. Resistance genes are not chromosomally linked. MDR-TB is defined as resistant to at least INH and RIF and, in some instances, to as many as seven antituberculosis agents.

Because administration of a single drug often leads to the development of a bacterial population resistant to that drug, effective regimens for the treatment of TB must contain multiple drugs to which the organisms are susceptible. When two or more drugs are used simultaneously, each helps prevent the emergence of tubercle bacilli resistant to the others. However, when the *in vitro* susceptibility of a patient's isolate is not known—which is generally the case at the beginning of therapy—selecting two agents to which the patient's isolate is likely to be susceptible can be difficult. Improper selection of drugs for the treatment of drug-resistant TB (i.e. providing only one drug to which most

organisms are susceptible) may subsequently result in the development of additional drug-resistant organisms.

The treatment options for MDR-TB are limited, since the majority of effective antituberculosis agents are compromised. The principles of treating tuberculosis are to start therapy with at least 4 drugs (INH, RIF, PZA, and either EMB or STM) unless the incidence of INH resistance in the area is < 4% (EMB or STM can be omitted). The physician should modify the regimen once susceptibility results are available (about 6 to 8 weeks). If the strain is susceptible, treatment should be continued for a total treatment course for at least 6 months.

When adherence with the regimen is assured, the four-drug regimen is highly effective even for INH-resistant organisms. Based on the prevalence and characteristics of drug-resistant organisms, at least 95% of patients will receive an adequate regimen (at least two drugs to which their organisms are susceptible) if this four-drug regimen is used at the beginning of therapy. Even with susceptible organisms, sputum conversion is accomplished more rapidly from positive to negative with a four-drug regimen than with a three-drug regimen.

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Part III
Problem Areas: Obstetrics

60
Chorioamnionitis

Chorioamnionitis is more than an inflammatory reaction of the placental tissues in response to organism invasion. In its clinical form, it is a threat to the maternal-fetal unit. The incidence of chorioamnionitis varies between 0.8 and 1.25 per 100 live births. A linear relationship between dissolution of fetal membranes and time selects for the presence of bacteria in amniotic fluid (infection) but not necessarily for disease in a cumulative pattern. The development of chorioamnionitis is not a simple corollary of prolonged rupture of the fetal membranes.

PATHOGENESIS

The fetal membranes, in conjunction with the cervical plug of pregnancy, constitute a formidable barrier to ascending infection. Nothing more than the extreme rarity of acute gonococcal endometritis/salpingitis disease after the eighth week of gestation despite a 5–6% incidence of subclinical gonococcal cervical infection is needed to document the effectiveness of this anatomical-physiological barrier in excluding vaginal commensal and pathogenic bacteria from the privileged sanctuary of the fetus. Once the fetal membranes are ruptured, the potential for ascending infection is great.

Approximately 7–12% of gravidas experience prolonged or premature dissolution of the fetal membranes. Of these, approximately 10–12% will develop chorioamnionitis. Ninety-six percent of the cases of chorioamnionitis are due to ascending infection. Hematogenous dissemination to the products of conception as a consequence of extragenital maternal septicemia accounts for 4% of the cases. The bacteria which can induce chorioamnionitis as a consequence of hematogenous dissemination include: *Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae, Salmonella typhi,* and the group A streptococci.

Perinatal sepsis, which is predominantly a reflection of fetal exposure to aerobic bacteria with augmented virulence as a consequence of ascending infection or of delivery through an infected birth canal, occurs in 1 % of neonates whose mothers' membranes were ruptured for more than 24 hours.

With the onset of labor and frank rupture of the fetal membranes, access to the fetus is simplified. The incidence of amniotic fluid infection is almost a direct function of time. When the fetal membranes have been ruptured for 24 hours, cultures of the amniotic fluid taken by the transabdominal route are bacteriologically positive in more than 65% of patients.

Infection of the amniotic fluid does not correlate closely with the successful establishment of infection in the fetus and perinatal sepsis. Amniotic fluid *per se*

constitutes a preferential aerobic microbiological environment. Since the exogenous pathogenic bacteria of man function primarily as aerobes, it is not surprising that there is a reasonable correlation between their presence in amniotic fluid and ensuing disease.

The presence of replicating organisms in amniotic fluid translates itself into intrauterine or neonatal infection in one of two ways:

(1) The bacteria are able to multiply sufficiently within the intra-alveolar spaces of the fetal lung so as to overwhelm the host defense mechanisms constituted by the alveolar-lining cells. Being part of the reticuloendothelial system, the alveolar-lining cells relegate this pathway to one of secondary importance.
(2) The major pathway for bacterial invasion involves direct penetration of the placenta. Once within the chorion, the bacteria gain potential access to fetal vessels. Fetal septicemia is due to arterial vasculitis. If the infection is prolonged, involvement of all three vessels can be demonstrated.

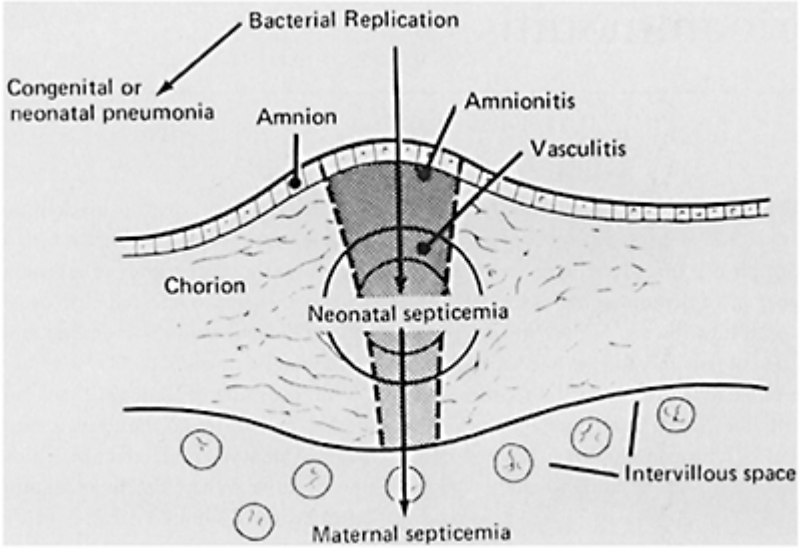

Figure 60.1 Potential infectious consequences of bacterial replication within the amniotic fluid (Blanc WA. *J Pediatr* 1961; 59:473)

As long as infection is limited to bacterial replication within the amniotic fluid, evidence of maternal involvement is limited. With involvement and penetration into placental arteries and/or the maternal implantation site, bacterial products such as endotoxins, as well as endopyrogens released from lymphocytes and neutrophils, may attain access to the fetal and maternal vascular compartments respectively (Figures 60.1 and 60.2). At this stage, maternal pyrexia, as well as fetal compromise (reflected primarily by abnormal heart rate changes) may occur. With the progression of the disease process, the fever

often rises sharply. Rigors are indicative of significant bacterial penetration into large maternal vascular channels.

MATERNAL INFECTIOUS MORBIDITY

Endometritis and endomyometritis

The factors which have a positive correlation with an increased incidence of uterine bacterial disease in patients undergoing Cesarean section are:

(1) the presence of selected class II-III anaerobes in amniotic fluid such as peptostreptococci and/or Bacteroidaceae (particularly in the presence of fresh meconium);
(2) the presence of exogenous pathogens such as *Neisseria gonorrhoeae;*
(3) the presence of endogenous bacteria with enhanced virulence such as the epithelial cell-adherent *Escherichia coli;* and
(4) the absence of intrapartum antibiotic therapy.

Patients with clinically overt anaerobic chorioamnionitis who deliver vaginally rarely develop endometritis; however, if the route of delivery is altered, even with the prophylactic administration of cephalosporin, a significant incidence of endomyometritis occurs. Of women who develop chorioamnionitis and receive antibiotic therapy prior to Cesarean section, approximately 15–30% develop postpartum endomyometritis in contrast to 60–75% who did not receive antibiotics.

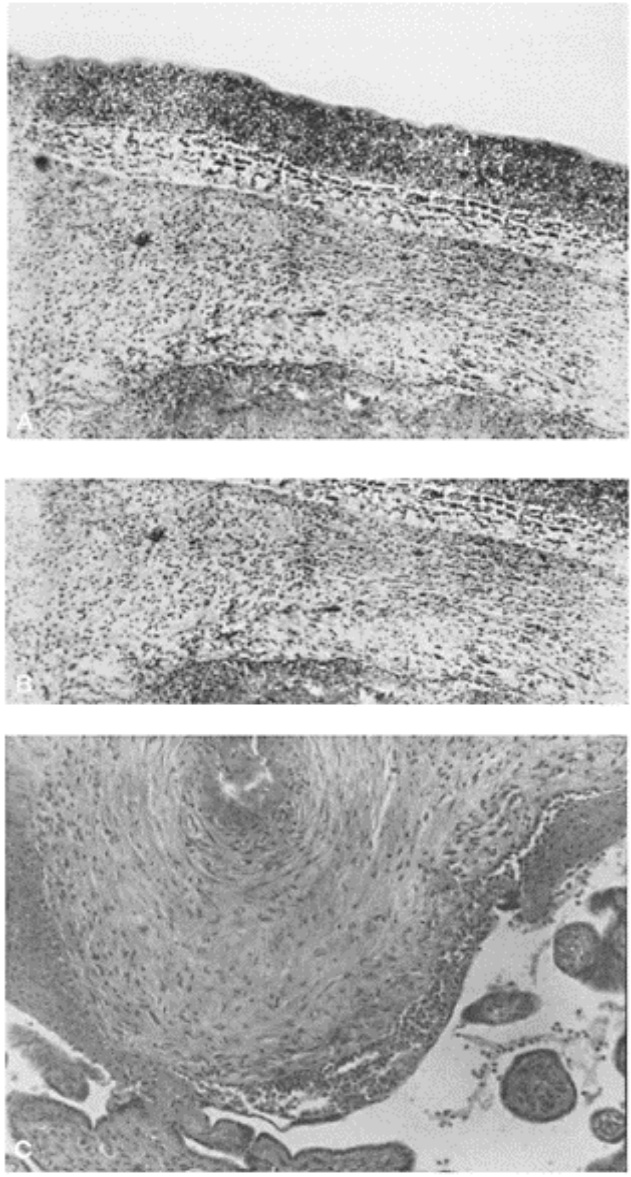

Figure 60.2 Histopathologic changes in chorioamnionitis. Above areas A and B are shown enlarged. **A.** Destruction of the amnion and an extensive acute inflammatory infiltrate invading the chorion, with transural

penetration of the large vascular channels at the lower limits of the photomicrograph (×320). **B.** Extension of the inflammatory process beyond the interstitium and the cytotrophoblastic layer, resulting in fibrin deposition within the maternal vascular compartment (arrow) (×520). **C.** Large photomicrograph, from which inserts A and B are taken, is stained with H&E (×65)

Maternal septicemia

Once significant penetration of the maternal vascular compartment is achieved, the circumstances are almost analogous to an individual's receiving an IV infusion of bacteria owing to:

(1) the inability of the site of penetration to be thrombosed; and
(2) the relatively unlimited substrate represented by the placenta.

Maternal septicemia is an indication for removal of the major nidus of bacterial replication. Therapy is directed:

(1) precluding metastatic bacteria complications (e.g. acute bacterial endocarditis); and
(2) uncoupling or eradicating the site of bacterial replication to avoid late sequelae such as intravascular coagulopathy and possible adult respiratory distress syndrome.

Analysis of maternal deaths associated with chorioamnionitis reveals two constants:

(1) the majority of etiological agents isolated are members of the Enterobacteriaceae; and
(2) most, if not all, of the deaths cited in the literature could have been prevented.

The three principal mechanisms for maternal demise in gravidas with chorioamnionitis are:

(1) septic shock due to the Enterobacteriaceae;
(2) *Clostridium* septicemia; or
(3) postpartum endomyometritis with septic thrombophlebitis.

In the context of modern day therapeutics, the maternal sequelae of chorioamnionitis are relatively limited. In a prospective study of 251 patients with premature rupture of the fetal membranes between 28 and 34 weeks gestation studied by Garite and Freeman, while 47 (19%) developed chorioamnionitis, there were no serious maternal sequelae. Similarly, Koh *et al.* have shown that the incidence of severe complications for the mother with chorioamnionitis has markedly decreased in recent years.

FETAL CONSIDERATIONS

Hyperthermia

Chorioamnionitis is a threat to the fetus by virtue of:

(1) the potential deleterious effects of hyperthermia on the fetal central nervous system; and
(2) induction of septicemia/pneumonia/meningitis by bacteria of enhanced virulence.

The fetus is in a positive heat-exchange situation with the mother across the maternal implementation site. When the maternal temperature is significantly raised and maternal hyperthermia sustained for any significant period of time, the gradient between fetal core temperature and maternal temperature increases. This increasing disparity between two temperatures results ultimately in a central nervous system demise of the fetus. A critical point of clinical management is maintenance of a maternal temperature below 38.6°C

Perinatal septicemia

Retrospective analysis of 79 perinatal septicemia cases from the Shands Teaching Hospital, Gainesville, Florida; University Hospital, Jacksonville, Florida; and Saint Joseph's Hospital, Omaha, Nebraska, demonstrates that 21% of neonates with documented septicemia in the first 24 hours of life were born to gravidas with chorioamnionitis and 53% were born to gravidas with prolonged rupture of the fetal membranes. When perinatal septicemia occurs, the bacteria are usually class I aerobic, endogenous organisms, *Escherichia coli* or the group B streptococci. Exogenous bacteria less frequently associated with perinatal septicemia include: *L. monocytogenes, H. influenzae, H. parainfluenzae, S. pneumoniae,* group A streptococci and selected enteric pathogens (e.g. *Salmonella typhi, Shigella*).

Table 60.1 Impact of intrapartum maternal antibiotic therapy on perinatal septicemia in patients with chorioamnionitis

	Intrapartum maternal antibiotic therapy	***No intrapartum maternal antibiotic therapy***
Percentage with perinatal or neonatal septicemia*	≥0–2.8%	≥5.7–21%

*Collective series of Gibbs *et al.,* Gilstrap *et al.,* Monif *et al.,* Sperling *et al.* (total # of cases 425)

Fetal morbidity and/or mortality is related not primarily to the causative agent but more directly to:

(1) the interim between onset of disease and institution of appropriate antibiotic therapy; and
(2) the gestational age of the fetus.

The ensuing morbidity and/or mortality is greater than 50% if therapy is not instituted within three hours of the onset of disease.

Perinatal septicemia due to peptostreptococci and Bacteroidaceae is a rare event which is usually of limited biological significance for the fetus.

In the absence of maternal antibiotic therapy for chorioamnionitis, the anticipated incidence of perinatal septicemia is 19–26%. If effective maternal therapy has been instituted for three hours or more prior to delivery, the incidence is markedly reduced (Table 60.1). When a case of perinatal septicemia occurs despite maternal therapy, it is due to a bacterial strain resistant to the antibiotic regimen used.

DIAGNOSIS

Terminology

In 1980, the term **intra-amniotic fluid infection** was introduced to describe clinical overt maternal-fetal infection. Since 1991, the term intra-amniotic infection has become interchangeable with clinical amnionitis and clinical chorioamnionitis. These terms, intra-amniotic fluid infection, clinical amnionitis and chorioamnionitis, are not totally identical clinical entities.

The criteria selected by the San Antonio group for designation of intra-amniotic infection were maternal fever (100.4ºF or higher) and rupture of the membranes, plus two or more of the following:

(1) maternal tachycardia;
(2) uterine tenderness;
(3) purulent, foul-smelling amniotic fluid;
(4) fetal tachycardia; and
(5) maternal leukocytosis.

Dorland's Illustrated Medical Dictionary defines infection as a term 'most often used to denote the presence of microorganisms within the tissues whether or not they result in detectable pathologic effects'. Disease is defined as 'a definite morbid process having a characteristic train of symptoms'. Chorioamnionitis encompasses intra-amniotic fluid and clinical amnionitis, but intraamniotic fluid infection is not necessarily chorioamnionitis. Only a minority of cases of intra-amniotic fluid infection progress to chorioamnionitis.

The secondary criteria advocated for the diagnosis of intra-amniotic fluid infection are sufficiently expansive that a given case series using these criteria may allow inclusion of cases, the pathogenesis and ultimate clinical significance of which may diverge significantly from the majority of cases compiled, e.g. maternal leukocytosis, maternal tachycardia in a gravida with fever and rupture of the fetal membranes does not equate with clinical chorioamnionitis with a one standard deviation probability.

Clinically overt intra-amniotic fluid infection in the form of anaerobic amnionitis may not have the same maternal and fetal clinical consequences as are observed in cases of chorioamnionitis due to primary class I bacteria. A significant number of infants with anaerobic amnionitis (foul-smelling baby syndrome) are born to gravidas with no systemic manifestations of infectious process. Only a rare neonate in this category ever

develops perinatal septicemia which, when it does occur, is usually of limited biological significance.

Another major problem with the current definition of chorioamnionitis is the prerequisite of rupture of the membranes for the diagnosis. This precludes inclusion of those cases of chorioamnionitis due to *L. monocytogenes, H. influenzae,* and *S. pneumoniae*, among others, which occur with intact fetal membranes secondary to hematogenous dissemination from the gravida to the products of conception. Approximately 4% of instances of chorioamnionitis with documented perinatal septicemia are due to these bacteria. Clinical recognition of this subgroup is critical since appropriate antimicrobial therapy can avert an adverse outcome.

In terms of histopathology, the term chorioamnionitis defines a demonstrable inflammatory process involving the chorion and amnion of the placenta. In terms of clinical utilization, the term denotes a disease, usually of bacterial etiology, involving the maternal-fetal unit. The clinician is not well served by any significant fusion of these two definitions. Patients with **clinically overt chorioamnionitis** almost invariably have a demonstrable inflammatory process within the placenta and membranes. The converse is not necessary or even frequently true. Gravidas who subsequently are demonstrated to have histological evidence of inflammation within the placenta are most often asymptomatic. To avoid confusion, the qualifying adjectives, histopathological and clinical, should be used to maintain conceptual integrity.

Infection vs disease

As long as the fetal membranes are intact and the gravida is not in labor, barring hematogenous involvement, cultures of amniotic fluid do not demonstrate the presence of either aerobic or anaerobic bacteria. With effective labor despite the presence of intact fetal membranes, bacteria, particularly anaerobic bacteria and the group B streptococci, may gain access to amniotic fluid. Once the fetal membranes are grossly disrupted, the probability of recovering bacteria from amniotic fluid increases almost linearly with time. After 24 hours, one or more bacteria can be recovered from the majority of amniotic fluids obtained by amniocentesis.

Maternal pyrexia

While the *de novo* development of fever in a gravida with ruptured membranes can have a large number of other etiological causes, chorioamnionitis must be the priority diagnosis of exclusion. In chorioamnionitis, maternal pyrexia is a host response to bacterial pyrogens which have reached the maternal intravascular compartment.

Maternal leukocytosis

The white blood cell count (WBC) tends to be more elevated in the pregnant female than in her nonpregnant match control or pre- or post-pregnancy level. A single elevated WBC is of little diagnostic significance. If serial WBCs are used to monitor a patient with prolonged or premature rupture of the fetal membranes, by the time a significant increase in the WBC is demonstrable, other clinical signs indicative of chorioamnionitis (i.e.

maternal pyrexia, sustained fetal tachycardia and/or uterine tenderness) are usually present. A marked increase in the maternal WBC usually indicates that bacteria have attained significant access to a maternal vascular site.

Bacteria in amniotic fluid

The presence of bacteria in amniotic fluid documents infection but not necessarily disease. The great majority of cases in which bacteria are recovered from amniotic fluid are from gravidas with no clinical evidence of disease. Bacterial quantitation is not a good predictor of the probability of ensuing chorioamnionitis. If more than or equal to 10^4 cfu of bacteria per ml of amniotic fluid are present, it has been contended that these gravidas are more likely to develop chorioamnionitis. Current data indicate that virulence of the organism, rather than its quantitative presence at a given point in time, is the principal factor selecting for disease.

Presence of white blood cells in amniotic fluid

An initial report by Larson *et al.* indicated that the presence of white blood cells in amniotic fluid correlated with the subsequent development of chorioamnionitis. Subsequent studies by Bobbitt and Ledger have largely put this concept to rest. The numerical scatter in their data is consistent with the concept that infection of the amnion is not uncommon. Infection as well as disease produces an inflammatory response of varying intensity.

Histological evidence of chorioamnionitis

There is at best a poor correlation between histological evidence of inflammatory changes involving the amnion, chorion and/or umbilical cord and clinical disease. Histological evidence of inflammation involving one or more placental components is not uncommon in patients with prolonged rupture of the fetal membranes. False-negatives may occur in the histological confirmation of disease.

Chorioamnionitis is a focal disease. Histological analysis of most placental tissue is often limited to a single section of the placenta (often randomly selected) and of the umbilical cord.

Foul smelling amniotic fluid

The presence of foul-smelling amniotic fluid does not necessarily indicate the presence of chorioamnionitis. What it does indicate is the replication of greater than 10^5 cfu of bacteria per ml of amniotic fluid due to polymicrobial bacterial flora in which anaerobic bacteria are dominant. Amniotic fluid is predominantly an aerobic microbiological environment. The presence of anaerobic bacteria in amniotic fluid has more clinical significance in terms of possible postpartum endomyometritis for the mother than in terms of neonatal or maternal septicemia.

Fresh meconium in amniotic fluid

The presence of fresh meconium is a signal of fetal distress and not necessarily of chorioamnionitis. Fetal distress may be the result of chorioamnionitis.

Specific signs

There are only two signs of chorioamnionitis which, by focusing directly on the maternal-fetal unit, increase the probability of an accurate diagnosis, namely:

(1) uterine tenderness; and
(2) persistent fetal tachycardia.

Uterine tenderness

Uterine tenderness can be easily confused with uterine irritability and resultant contractions, hence the need for serial observation and early confirmation by a skilled examiner.

Persistent fetal tachycardia

Persistent fetal tachycardia is the one criterion almost universally accepted. A point of contention has been what constitutes fetal tachycardia. Fetal tachycardia is defined as a fetal heart rate of 160 beats per minute for 5 minutes in the absence of maternal medications and maternal pyrexia greater than 38.6°C.

The criteria for the diagnosis of chorioamnionitis are the presence of TWO of the following THREE clinical signs of disease:

(1) maternal pyrexia (non-specific). A confirmed temperature of greater than 37.8°C;
(2) uterine tenderness (specific); and
(3) persistent fetal tachycardia (specific). A fetal heart rate greater than or equal to 160 beats per minute for 5 minutes.

The assessment of all clinical criteria is readily attainable and requires no additional expenditure of healthcare dollars. This potentially can be done under relatively primitive conditions outside of large medical centers.

Cultures

The urinary tract, endocervix, and amniotic fluid should be sampled for identification of a possible etiological agent. Bacteria which successfully adhere to uroepithelial cells and are present in $\geq 10^5$ cfu/mg of urine are bacteria of enhanced virulence and must be effectively covered by the antibiotic regimen selected. Sexually transmitted disease pathogens need to be effectively excluded from diagnostic consideration. To do so, the endocervix must be appropriately sampled for viable organisms or their antigenic

equivalents. Unless the amniotic fluid is foul smelling, only aerobic cultures are required. Despite the presence of fever, blood cultures are of limited value.

Locksmith and Duff reviewed the records of 539 patients with chorioamnionitis who delivered over a three year period. Thirty-nine of 538 patients, 7.2%, had positive blood cultures. In only one of the patients did the blood culture result definitively alter therapy. This patient had a fever of unknown origin, and the blood culture led ultimately to the diagnosis of chorioamnionitis. The mean duration of febrile morbidity was not significantly different in the bacteremic vs. non-bacteremic patients, 2.03 vs. 1.74 days. None of the repeat blood cultures were positive. The cost of blood cultures in this study population was $72759.

THERAPY

Chorioamnionitis is a mandate for maternal and fetal therapy. The antibiotic selected must:

(1) be broad enough to encompass the aerobic pathogenic spectrum delineated; and
(2) adequately address the issue of bioavailability to the fetus (be able to traverse the placental barrier in therapeutic concentrations).

Drug of choice for fetal therapy is ampicillin or piperacillin. The reasons for the selection of an aminopenicillin (ampicillin) or ureidopenicillin (mezlocillin or piperacillin) as drugs of choice are safety for the fetus, bioavailability and spectrum of efficacy.

Ampicillin lacks coverage for selected Enterobacteriaceae (*Klebsiella pneumoniae*, 20–30% of *E. coli*, *Serratia* and *Enterobacter species*) and the penicillin-resistant Bacteroidaceae. Mezlocillin and piperacillin are potentially therapeutic for only 40–50% of the strains of *K. pneumoniae* and *Klebsiella* species. If foul-smelling amniotic fluid is present, an intravenous bolus of metronidazole may be utilized for coverage of the Bacteroidaceae. The relative inability of clindamycin to effectively traverse the placental barrier limits its theoretical efficacy. Although chloramphenicol readily crosses the placental barrier, the inability of the neonate to detoxify the drug with the ensuing clinical corollary, ‘gray baby syndrome’, absolutely contraindicates its administration.

Monoetiological chorioamnionitis due to either hematogenous or ascending infection can be cured *in utero*. The major problem with fetal therapy is the inability to cover the entire pathogenic spectrum, particularly of the Enterobacteriaceae. Selected third generation cephalosporins appear to have the ability of attaining therapeutic levels in cord blood and amniotic fluid. These antibiotics may become incorporated into fetal therapy owing to their augmented coverage of the Enterobacteriaceae; however, they lack efficacy for *L. monocytogenes*.

Drug of choice for maternal therapy is an aminoglycoside. In the majority of gravidas with chorioamnionitis who developed septic shock, an Enterobacteriaceae, usually *E. coli* or *K. pneumoniae,* functioned as the principal causative agent.

The key to therapy is early recognition of chorioamnionitis and the early institution of therapy. The later clinical intervention occurs, the greater the potential for augmented morbidity and possible neonatal and/or maternal demise.

One of the major questions which has yet to be adequately addressed is that of whether or not there is such a thing as *in utero* therapy. Hematogenously acquired chorioamnionitis due to *L. monocytogenes* has been successfully treated *in utero*. With premature rupture of the membranes, one has open access to a diverging bacterial flora. Monif has described a patient with premature rupture of the membranes, recurrent chorioamnionitis and maternal septicemia due to group G streptococci whose initial episode occurred at 22 weeks. Because of the excellent maternal and fetal response and the inability to abort the fetus, the adoption of a conservative management program was forced. The patient continued to leak amniotic fluid and returned at 29 weeks with renewed evidence of chorioamnionitis and of septicemia due to *E. coli* and *K. pneumoniae*. *Escherichia coli* was also grown from amniotic fluid, placenta and urine. Because of the inability to reverse fetal signs of chorioamnionitis with antibiotic therapy, the baby was delivered vaginally. The resultant 1090 gram infant survived a stormy neonatal course and, at one year of age, was clinically normal with the exception of oxygen-induced retinopathy.

MONITORING OF PROLONGED RUPTURE OF THE FETAL MEMBRANES (PROM) FOR INFECTIOUS COMPLICATIONS

One must presume that the majority of gravidas with documented rupture of the fetal membranes greater than 12 hours and a significant number of gravidas who have labored extensively have bacteria present within the amniotic fluid. One must exclude bacteria of enhanced virulence in order to focus tightly on the optimal perinatal plan for both mother and fetus. Management of these patients involves excluding the presence of the following bacteria:

(1) urinary tract pathogens;
(2) groups A, B, C and G beta-hemolytic streptococci; and
(3) *Neisseria gonorrhoeae.*

The use of a group B beta hemolytic streptococcus (GBS) effective antibiotic does not negate the need for selective microbal monitoring.

Bacteriological screening

Urinary tract bacterial isolates

Any gravida with any of the following:

(1) prior documented asymptomatic bacteriuria in pregnancy;
(2) a history of prior urinary tract infections in pregnancy;
(3) frequent urinary tract infections in the pre- and/or post-adolescent years; or
(4) no prenatal care

should have a screening nitrite test and leukocyte esterase analysis, as well as urine culture done immediately upon admission. If the nitrite test is positive, repeat the test. If

again positive, we advocate placing the patient on a third generation cephalosporin which has FDA approval for Gram-negative meningitis. If the nitrite test is negative, but the culture is positive, the choice of antibiotics is predicated upon Gram stain of the urinary sediment. If a Gram-positive isolate is identified, ampicillin is administered in lieu of the third generation cephalosporin.

Beta hemolytic streptococci

Gravidas with ruptured fetal membranes and any of the following:

(1) a beta-hemolytic streptococcus previously isolated;
(2) prior neonatal disease or demise due to the group B streptococcus;
(3) an immature or premature gestation;
(4) an unfavorable cervix; or
(5) no prenatal care

need to be presumed to be infected and managed in accordance with GBS neonatal disease avoidance programs.

Neisseria gonorrhoeae

At the time of admission to labor and delivery, if the physician is dealing with a term gestation a more conservative approach can be initiated. If a test is positive for *Neisseria gonorrhoeae,* the mother should receive a cost-effective third generation drug which is resistant to plasmid-mediated beta-lactamases and capable of traversing the blood-brain and presumably the placental barrier. While one dose is probably sufficient to eradicate maternal colonization, potential problems in terms of drug availability in therapeutic concentrations within amniotic fluid argues for more than one dose therapy.

Biochemical testing

The only laboratory value which has been of any assistance in identifying possible disease in evolution has been the C-reactive protein (CRP). The negative predictive value of CRP determination is greater than the positive predictive value. Once the CRP value becomes positive before delivery in a patient with PROM, the test is of limited added value. If chorioamnionitis does develop and a commitment to *in utero* therapy is made in case of an immature-premature infant, serial CRP determinations again become of value in guiding the duration of therapy. It is our policy to continue antibiotic therapy 24 hours beyond a negative titer.

Once the cultures are obtained under sterile conditions, no further pelvic examination is to be done unless umbilical cord prolapse is suspected.

Presuming that all baseline cultures are negative, we advocate establishing a monitoring regimen which includes temperature, fetal biophysical profile, fetal heart rate, assessment of uterine tenderness and CRP. These parameters dictate the subsequent clinical management.

Clinical monitoring

Superimposed upon bacteriological monitoring and/or prophylactic antibiotic administration is careful clinical monitoring.

The patient should be monitored closely every one to four hours for one or more clinical signs of disease:

(1) maternal pyrexia (non-specific). A confirmed temperature of greater than 37.8ºC;
(2) uterine tenderness (specific); and
(3) persistent fetal tachycardia (specific). A fetal heart rate greater than or equal to 160 beats per minute for 5 minutes.

If one of the above criteria becomes abnormal, the interim of monitoring for all parameters is cut in half or preferably to an hourly occurrence. The appearance of a second abnormal parameter constitutes the basis for the diagnosis of chorioamnionitis.

If the patient has a favorable Bishop score and a viable fetus, delivery by the vaginal route can be attempted. A general rule of thumb is ‘don’t get a failed delivery with induction in a sick baby’. Guidelines favoring the prompt termination of pregnancy include:

(1) a non-responsive stress test and a positive oxytocin challenge test;
(2) fetal bradycardia;
(3) fresh appearance of meconium with any concomitant evidence of fetal compromise;
(4) evidence of maternal decompensation or worsening of maternal disease; or
(5) increasing maternal pyrexia despite antibiotic therapy of 120 minutes duration.

Gravidas with premature and PROM who develop chorioamnionitis while under clinical monitoring and who are clinically stable with an immature fetus which is greater than 22 weeks may be candidates for what has been termed an ‘antibiotic therapeutic challenge’.

Aggressive therapy with a ureidopenicillin and an aminoglycoside is instituted. If there is total lysis of fever and documented resolution of all other abnormal parameters within three to four hours of the initiation of antibiotic therapy, subsequent management of the mother and fetus is as if chorioamnionitis had never occurred. Failure of any of the maternal or fetal clinical criteria to respond to antibiotic therapy within four hours, particularly failure of fetal tachycardia to abate or the appearance of variable decelerations with a non-responsive stress test, argues for prompt termination of pregnancy. This approach is controversial and requires maternal acceptance of the potential grave risks involved.

Prevention

Prophylactic use of antibiotic therapy to prevent chorioamnionitis and perinatal septicemia has gained broader acceptance. The criteria developed for GBS early-onset disease prevention have broader applicability. The following settings identify gravidas at risk for more than perinatal GBS sepsis:

(1) Preterm rupture of fetal membranes;
(2) PROM12–18hours;or

(3) gravidas with ruptured membranes who has had recurrent asymptomatic bacteriuira or urinary tract infections.

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61
Infectious morbidity associated with intrauterine monitoring

Intrapartum fetal monitoring has become a standard procedure for the evaluation of fetal well-being during labor. The passage of a mechanical conduit through a non-sterile area and the application of a scalp electrode to the fetal head introduce the potential for augmented fetal infectious morbidity. There is no statistically significant increase in the maternal infectious morbidity. The risks to the mother are basically those inherent in the situation, for example, premature rupture of the fetal membranes and labor or the presence of *Neisseria gonorrhoeae* or group A streptococci as part of the vaginal flora. The combination of rupture of the membranes and labor, aside from the presence of exogenous pathogens in the vaginal flora, is the major risk factor for both the frequency and the severity of maternal infection. Once the membranes are ruptured, internal monitoring does not appear to add to the risk for the gravida. The scalp electrode *per se* has created a new infectious complication for the fetus, namely, abscess formation at the site of attachment. The incidence of scalp abscess is of the order of 1:200 to 1:400 monitored patients. While scalp abscesses have been noted with both the clamp-on type and the spiral electrode, spiral electrodes with a barb at the tip may have been associated with a higher incidence. Fortunately these types of spiral electrodes are no longer clinically employed.

In many instances, there is no correlation between neonatal scalp abscesses and the number of electrode applications, duration of monitoring, or concurrent amnionitis. The pathogenesis of scalp abscesses requires not only a mechanical disruption of the cutaneous barriers but also, presumably, a laceration of an arterial or venous vessel with secondary microhematoma formation. The bacteria isolated from such lesions are predominantly Gram-positive cocci. Both the aerobic (coagulase-negative staphylococci, *Staphylococcus aureus*, group B and D streptococci) and the anaerobic (peptostreptococci) cocci have been recovered from scalp abscesses. An unusual but significant pathogen has been *Haemophilus influenzae* type B. Less frequently, members of the Enterobacteriaceae or Bacteroidaceae (particularly *Bacteroides fragilis*) have been present. The high incidence of so-called ‘sterile acute scalp abscesses’ attests to the important role played by obligate anaerobes in the more advanced lesion and the failure to use appropriate anaerobic technology to isolate and identify these agents. Specimens for bacteriologic analysis should be obtained by aspiration, with care so as not to draw up any air. If this is not possible, one should submit a fragment of necrotic tissue in a sterile container.

Characteristically, disease is manifested in the first eight days of life. Abscess is usually the clinical presentation. In the absence of septicemia, the infant is afebrile. The treatment of a scalp abscess is basically complete incision and drainage under antibiotic coverage after appropriate cultures have been taken and a representative specimen has been Gram stained. Serious sequelae such as septicemia and osteomyelitis may occur. If osteomyelitis ensues, craniotomy and excision of the area of infection may be required.

In rare instances, a progressive cutaneous gangrene not dissimilar to a Meleney type II ulcer may occur. In such cases the tissue destruction extends down to the periosteum (Figure 61.1). A scalp abscess should not be treated lightly; isolated case reports of neonatal demise are present in the literature in which the site of the scalp electrode provided the portal for lethal infection.

While providing a portal primarily for bacterial infection, scalp electrodes, on rare occasion, may provide a portal of entry for other types of pathogens. Adams

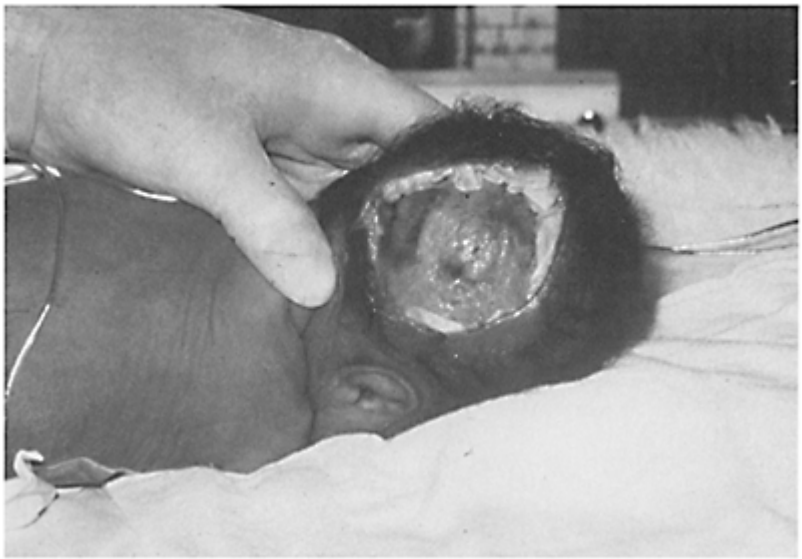

Figure 61.1 Progressive cutaneous gangrene. Cutaneous slough measuring 8×8 cm and extending to the periosteum due to necrotizing fasciitis which originated at the site of the fetal scalp electrode. (Feder HM Jr *et al. J Pediatr* 1976; 89:808)

et al. reported scalp infections with herpes simplex type 2 virus at the monitor probe site. Similarly, Golden *et al.* have reported a case of fatal disseminated neonatal herpetic infection in which the initial clinical manifestation occurred at the site of a fetal scalp electrode.

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62
Postpartum endometritis/ endomyometritis

While endometritis following spontaneous vaginal delivery is a relatively rare event, endomyometritis is a common postpartum complication following Cesarean section. If prophylactic antibiotics are not used, the incidence of post-cesarean endomyometritis varies from a low of 15% to a high of 65%. In general, the lowest incidence of infection occurs in middle- and upper-income women undergoing scheduled elective abdominal delivery; the highest incidence of infection occurs in young, indigent patients having surgery after extended duration of labor and ruptured fetal membranes. Use of prophylactic antibiotics at the time of abdominal delivery usually reduces the number of postoperative infections by approximately 50 to 60%. Approximately 15% of women with endomyometritis will have a documented bacteremia. If disease is not aggressively treated, pelvic abscess, septic thrombophlebitis, septic shock and adult respiratory distress may ensue.

PATHOGENESIS

The understanding of the pathogenesis of endometritis requires analysis of selected demographic facts. Following spontaneous vaginal delivery, 1–4% of women develop postpartum endometritis. The higher incidence of disease occurs in women from disadvantaged backgrounds or women who have had no antenatal screening for *Neisseria gonorrhoeae,* asymptomatic bacteriuria or the group B streptococci. If the mode of delivery is changed to an abdominal one, the incidence of disease is 10 to 15 fold that observed in patients delivering vaginally (Figure 62.1). The bacteriology of these two groups is significantly different. In the cases of endometritis, in excess of 90% of the isolates are aerobic pathogens encompassed in groups I and IV of the Gainesville Classification. Included are both exogenous pathogens (e.g. group A, C, and G streptococci, *Neisseria gonorrhoeae, Haemophilus influenzae*) and endogenous pathogens (e.g. group B streptococci and the Enterobacteriaceae). Less than 10% of cases involve polymicrobial infection. These latter cases are often associated with retained products of conception or obstetrical trauma. In excess of 90% of cases of endomyometritis are the consequence of the anaerobic progression.

Since the advent of modern microbiology, we have asked ourselves the question, ‘Why do certain women develop postpartum endometritis or endomyometritis?’ The introduction of sophisticated anaerobiology has documented the shallowness of our own conceptual thoughts. With appropriate anaerobiological techniques, we can demonstrate the almost universal presence of bacteria in the endometrial cavity of women following spontaneous vaginal delivery. Seventy to 80 percent of patients can be demonstrated to have moderate ($>10^6$ cfu/g) or heavy growth ($>10^9$ cfu/g) of at least one bacterial species.

The incidence of positive cultures is progressive with time. Whitacre *et al.* found that all endometrial cultures will be positive after 24 hours and that this type of endometrial infection persisted for at least five days. Clotted blood and necrotic decidua provide ideal culture media for anaerobic bacteria. An open cervical patulous cervix constitutes an open conduit for the vaginal bacterial flora.

Why do only 1–4% of women delivering vaginally and without obstetrical trauma go on to develop disease, more specifically, endometritis? Why doesn't every woman develop endometritis in the postpartum period, since bacteriological studies have documented the almost universal presence of bacteria within material obtained by transabdominal aspiration in the immediate

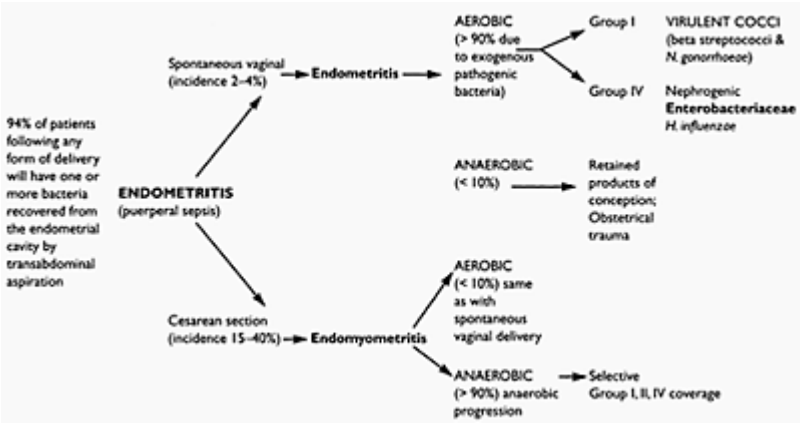

Figure 62.1 Impact of mode of delivery on incidence of infectious complications and microbiology of disease. From Monif GRG. *Infectious Disease Care Manual—Obstetrics*, 4th edition. Gainesville, FL: IDI, 1988

postpartum period? Based on a purely qualitative bacteriological assessment of the endometrium, uninfected patients cannot be distinguished from those with postpartum endometritis unless an exogenous pathogen, i.e. group A streptococci or *Neisseria gonorrhoeae*, is present. The mere presence or replication of bacteria within necrotic decidua is not sufficient to produce disease. Underlying the necrotic decidua and clotted blood is a layer of healthy endometrial tissue, the oxidation-reduction potential of which usually precludes the penetration of class II and class III anaerobes. Microaerophilic class II and class III anaerobes do not represent a significant cause of postpartum endometritis following spontaneous vaginal delivery; however, if retained products of conception still have continuity with the placental implantation site, the vascular access thus provided circumvents the endometrial basalis barrier. Similarly, when significant obstetrical trauma has occurred and laceration extends through the endocervix, the associated

bleeding, coupled with the availability of bacterial flora, creates ideal conditions for the immediate anaerobic syndrome to ensue.

In the course of performing a Cesarean section, the basalis layer of the endometrium is iatrogenically disrupted. The devitalized tissue (resulting from clamping, loss of its vascular supply, and coagulation) coupled with microhematoma formation along the line of tissue reapproximation not only create conditions favorable for anaerobic bacterial replication but also circumvent the principal anatomical barrier to anaerobic infection. While intra-amniotic fluid infection caused by selected class I anaerobes tends to select for chorioamnionitis, the presence of class II anaerobes, i.e. peptostreptococci and Bacteroidaceae, is apparently a partial catalytic factor in the induction of endomyometritis in the absence of virulent class I anaerobes.

DIAGNOSIS

The diagnosis of endometritis or endomyometritis is often difficult to make. Fever is the cardinal manifestation of disease. Standard puerperal morbidity is defined by the Joint Committee on Maternal Welfare as ‘a temperature of 100.4°F (38.0°C) occurring in any two of the first ten days postpartum, exclusive of the first 24 hours’. Exclusion of the first 24 hours is predicated upon the observation that, following spontaneous vaginal delivery, 6–8% of women will have an isolated febrile spike in the first 24 hours; however, only a quarter to one-third of these individuals will develop overt diseases requiring antibiotic therapy.

The probable reason for the isolated febrile spike is closure of the cervical os by a large necrotic decidual fragment. The reason for the spontaneous resolution of fever is passage of the fragment secondary to uterine contractions and re-establishment of surgical drainage. In patients who have undergone general anesthesia for Cesarean section, fever in the first 24 hours is often attributed to ‘atelectasis’. If serial blood gases are done on patients who undergo radical abdominal surgery for four hours, 100% will have evidence of alveolar-perfusion dissociation and 10–12% will have demonstrable linear atelectasis on chest roentgenogram, yet only a small percentage of these patients will develop fever.

The indications for fever workup in the postpartum woman are:

(1) two consecutive temperatures greater than or equal to 38ºC taken at least four hours apart with the second temperature greater than 0.2ºC higher than the first;
(2) one temperature greater than 38.5ºC; and
(3) three temperatures greater than or equal to 38ºC in any 24 hour period.

The adoption of a policy of aggressive early intervention lessens the likelihood that other corroborating signs, e.g. uterine tenderness or purulent lochia, will be present. A moderate degree of clinical experience is required to distinguish the uterine tenderness engendered by the operative procedure from that associated with endometritis. The presence of a foul-smelling discharge may occur in cases of long standing duration (usually associated with retained products of conception). The primary goal of the physical examination is not to corroborate the diagnosis of endometritis or endomyometritis, but rather to rule out a non-operative site of infection.

Unless the process is due to documented pathogens, the bacteriological results engendered by culturing the endometrial cavity flora provide marginal information. To culture the endometrial cavity, a swab must traverse the vagina and endocervix, both of which possess a bacterial flora. The way the swab is used and the way the bacteriological specimen is handled will influence the spectrum of bacteria recovered and the interpretation of data. The real reason for taking an endometrial culture is not to identify the anaerobic bacteria functioning in the anaerobic progression, but to rule out the presence of bacteria of unique virulence (e.g. group A streptococci, *Neisseria gonorrhoeae*) whose identification impacts beyond immediate patient care.

Utilization of anaerobic methodology does not preclude the identification of aerobic or facultative anaerobic bacteria, whereas the converse is not true. The request for anaerobic culturing of endometrial swab material is a misuse of the microbiological facility. Even if an anaerobic swab is utilized, by being withdrawn back into the vaginal environment, it is exposed to sufficient oxygen to eradicate any class III anaerobes which may be present.

When obtaining a culture which may be expected to yield anaerobic bacteria, it is important to make a Gram stain at the time of the bacteriological sampling and compare it to the Gram stain and bacterial isolate derived from the microbiology laboratory. The demonstration of bacteria on Gram stain which fail to grow on synthetic media indicates the presence of class III anaerobes.

Whether or not blood cultures should be obtained in every case of endometritis or endomyometritis is a point of controversy. The anticipated incidence of positive blood cultures is approximately 4–15%, depending upon the number of sets of blood cultures taken. The bacteriological data engendered by positive blood cultures influence therapy in less than one percent of cases. Our policy has been not to obtain blood cultures in a postpartum woman unless:

(1) her temperature exceeded 39ºC; or
(2) she appeared to be in some degree of clinical difficulty.

To deal with cost issues it is important that each institution develop its own guidelines.

THERAPY

Endometritis following spontaneous vaginal delivery

If obstetrical trauma or the presence of retained products of conception can be ruled out, the probable prime etiological agents are exogenous bacterial pathogens: the virulent cocci (groups A, C, G streptococci or *Neisseria gonorrhoeae*) or the nephrogenic Enterobacteriaceae (*Escherichia coli* or *Klebsiella pneumoniae*). The group B streptococci, though endogenous bacteria, are a frequent etiological agent for early-onset endometritis (disease manifestation in the first 12–18 hours postpartum). Antibiotic coverage for endometritis following spontaneous vaginal delivery can best be achieved by Category I and IV therapy, i.e. ampicillin and an aminoglycoside. If the anticipated therapeutic response fails to develop, a third antibiotic effective against the non-penicillin-sensitive Bacteroidaceae needs to be used.

If obstetrical trauma or retained products of conception are present, greater coverage must be afforded against Category II bacteria capable of functioning in the anaerobic progression.

Endomyometritis following abdominal delivery

The combination of penicillin or one of its semisynthetic analogues with an aminoglycoside leaves an antibiotic gap in Category II of the Gainesville Classification, the penicillin-resistant Bacteroidaceae.

What are the consequences of antibiotic failures due to this family of bacteria? The consequences of a Category II gap in the treatment of endomyometritis following Cesarean section are:

(1) septic thrombophlebitis; and
(2) pelvic abscesses.

A small percentage (2–4%) of patients develop very serious pelvic infection or septic thrombophlebitis. Gibbs *et al.* analyzed 160 patients treated with penicillin and an aminoglycoside. Seventy-eight percent of 135 patients were cured. Twenty-eight of their 35 therapeutic failures responded to clindamycin or chloramphenicol. Seven patients (4%) developed abscesses or septic thrombophlebitis. Of the 100 patients treated by diZerega *et al.* with penicillin and gentamicin, one patient developed a pelvic abscess necessitating hysterectomy, and two responded to heparin challenges. Among the 50 patients treated with penicillin and kanamycin at the Shands Teaching Hospital of the University of Florida, four developed septic thrombophlebitis, and one had a pelvic abscess which required surgical intervention. When antibiotic coverage encompasses the non-penicillin-sensitive Bacteroidaceae, serious complications, specifically pelvic abscess or septic thrombophlebitis, are virtually eliminated.

Endomyometritis, particularly in those cases complicated by septic thrombophlebitis or pelvic abscesses, was once a major cause of maternal mortality and morbidity. With the modern day antibiotics, one can anticipate an 89–93% arrest of disease with literally any antibiotic combination which impacts significantly on Categories I, II and IV of the Gainesville Classification. When dealing with the early phase of the anaerobic progression, effective therapy will render the temperature less than 37.6ºC and result in resolution of local physical findings within 24 hours.

What is important is the physician’s ability to deal with the failure to obtain the anticipated therapeutic response in 24 hours. If the anticipated therapeutic response does not develop within 24–36 hours, reexamine the patient. If the initial clinical diagnosis is still the working diagnosis and retained products of conception are not found on pelvic examination, close the existing bacterial gap of the Gainesville Classification with appropriate antimicrobial therapy. If the anticipated therapeutic response does not develop within 24 hours, discontinue all current antibiotics and place the patient on intravenous metronidazole if previously on clindamycin or vice versa. If fever does not lyse in 24 hours, commence heparin challenge unless there are specific localizing signs. If the fever persists despite metronidazole therapy and heparin challenge, the probability of surgical intervention should be assessed.

The concept of triple therapy coverage plus heparin challenge was developed to cleave medically treatable disease from disease requiring surgical intervention.

Failed prophylaxis endomyometritis

The prior antibiotic use in the immediate pre-operative or perioperative period influences antibiotic selection. When a cephalosporin has been used, it is impossible to close the remaining categories of the Gainesville Classification with the addition of clindamycin and an aminoglycoside. In this situation aggressive therapy usually entails 'triple therapy' or triple therapy equivalent (e.g. ampicillin-sulbactam, piperacillin-tazobactam acid or imiperem-cilastatin). If ampicillin is used, the drug effectively impacts on categories I and III. The gaps in the Gainesville Classification can be effectively closed with clindamycin or metronizadole and an aminoglycoside. If a patient develops endomyometritis following antibiotic prophylaxis, do not incorporate into the subsequent therapy the drug used for prophylaxis or a closely related antibiotic.

CHRONIC ENDOMETRITIS

Endometritis occurring in the absence of parturition or a recent surgical procedure is usually the consequence of ascending infection (i.e. *Chlamydia trachomatis*), endocervicitis associated with an abnormal vaginal flora, foreign body induced (i.e., intrauterine device (IUD)related) or retrograde spread from the fallopian tubes *(Mycobacterium tuberculosis, Actinomyces israelii).*

The earliest manifestation of occult endometritis is the occurrence of so-called 'breakthrough' bleeding. Intermenstrual bleeding, especially in a patient previously well regulated on birth control bills warrants aggressive evaluation to exclude endometritis due to a sexually transmitted disease. Krettek and Monif described this syndrome. The predominant cause of this finding in their series was infection with *C. trachomatis*. The second most common etiology was vaginal bacteriosis with or without the concomitant presence of *Trichomonas vaginalis*. As in Burnhill's syndrome (IUD-related bacterial endometritis; Chapter 70) the sudden appearance of inflammatory cells can alert the clinician as to the possibility of an infectious process within the endometrium.

With disease progression, intermenstrual menstrual discharge and some degree of cervical motion tenderness will develop well before grossly discernible changes in uterine configuration. What additional signs or symptoms develop is a function of the underlying disease process.

Documentation of the presence of an endocervicitis requires a uterine aspiration biopsy. Such a biopsy can be best obtained using a Pipelle-like apparatus. Part of the specimen, not sent for culture, should be place in 10% formalin and submitted for histological analysis. When doing a biopsy, it is best to avoid the first few days after a period or those immediately before the onset of menstruation.

An alternate approach, which may infer the diagnosis, involves obtaining a swab of the uterine cavity using a sheathed swab. The presence of inflammatory and/or plasma cells is presumptive evidence of endometritis. Great care most be given to the manner in which the specimen is collected. A chronic endocervicitis is relatively common.

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Septic pelvic thrombophlebitis

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The physiological changes attending pregnancy fulfill the requisites of Virchows triad (circulatory stasis, vascular damage and hypercoagulability of blood). Factors VII, VIII and X are increased in pregnancy. Postpartum or postoperative infections of the female genital tract by the release of thrombin-mediated fibrin may induce septic pelvic thrombophlebitis.

The prevalence, which varies according to the extent of operative trauma, occurs ten times more frequently in women who have undergone Cesarean section or septic abortion than in women who have delivered vaginally. Aggressive use of antibiotics in infection avoidance schema has rendered its occurrence even less likely. When endomyometritis does occur, failure to cover for the penicillin-resistant Bacteroidaceae and *Prevotella* (Category II of the Gainesville Classification), results in an increased prevalence of this post-surgical complication (2–4%). If initial therapy is complete for the anaerobic bacteria, the incidence among cases of endometritis and endomyometritis is less than 0.5%. Pelvic vein thrombophlebitis occurs once in 2000 spontaneous vaginal deliveries, approximately 10–20 times less frequently than after Cesarean section.

Septic thrombophlebitis in the obstetric patient evolves in one of three clinical settings:

(1) in association with retained products of conception and anaerobic infection;
(2) after Cesarean sections in which endomyometrial bacterial invasion attains vascular access; or
(3) with criminal abortion.

In gynecologic patients, septic thrombophlebitis is observed in association with ovarian abscess, tubo-ovarian abscess with involvement of the ovarian parenchyma, ligneus cellulitis, and postoperative gynecologic infections.

PATHOGENESIS

In septic thrombophlebitis, bacterial infection causes an inflammatory process within the vein and ensuing thrombus formation. The process extends from thrombosed sinuses involving continuous uterine and/or ovarian veins. In advanced cases, involvement of the iliac veins, inferior vena cava, and renal vein may occur.

From these foci, septic thromboemboli are sloughed off, resulting in intermittent septicemia, pulmonary emboli, and potential metastatic abscess formation. The bacteria most commonly involved are the peptostreptococci and Bacteroidaceae/Prevotella, acting singularly or in combination.

CLINICAL PRESENTATIONS

Pelvic vein thrombophlebitis has three characteristic patterns:

(1) pelvic infection with evidence of hematogenous metastatic complications;
(2) persistent fever of undemonstrable etiology after therapy for pelvic infection; or
(3) ovarian vein variant.

The most common clinical presentation of pelvic vein thrombophlebitis is fever of unknown origin with no demonstrable focus of infection. Pelvic thrombophlebitis as a cause of fever of obscure etiology was a concept introduced by Michaelis in 1911 (Michaelis's sign).

Table 63.1 Protocol for the heparin challenge test

1. Test for activated partial thromboplastin time (aPTT) and platelet count.
2. Weigh the patient.
3. Select heparin loading dose and infusion rate. Order 25000 units in 500 ml of 5% dextrose in water (D5W). Begin infusion 1 hour after loading via your choice of pump. Begin infusion within 1 hour after bolus.
4. Obtain aPTT 6 hours after initiation of continuous IV heparin drip. Because the half-life of heparin is 40 to 80 minutes, patients should reach a steady state 4 to 8 hours after infusion.
5. Increase or decrease drip by 100 to 200 units/h until aPTT is double the normal values (approximately 55 seconds). To determine whether steady state has been achieved, obtain a repeat aPTT at 4 and 8 hours allowing the drug to persist through at least four half-lives.
6. Once aPTT is in a therapeutic range and a steady state has been documented daily, a complete blood count and platelet count usually suffice. After the therapeutic dosage has been established, it is seldom necessary to readjust the infusion rate.
7. If aPTT substantially exceeds the therapeutic range,give 50 to 100 mg of protamine by IV bolus. An alternative regimen is to give 1 mg of a 1% solution of protamine sulfate for every 100 units of heparin in the patient's body.

The diagnosis is difficult because fever is often the only physical finding present unless septic pulmonary infarcts develop as a consequence of peripheral embolization of infected clots.

Rigors (frank chills) are not commonly associated with septic thrombophlebitis in a post-partum patient unless disease is the consequence of retained products of conception at the maternal implantation site.

DIAGNOSIS

The diagnosis of septic thrombophlebitis requires a high index of suspicion: infectious morbidity framed in the appropriate clinical setting. The patient usually has an ongoing infectious process in the pelvis either *de novo* or in conjunction with surgical intervention for benign or malignant disease. The diagnosis is most commonly inferred when a patient

continues to have fever despite complete four-category coverage as determined by the Gainesville Classification. A picket-fence fever curve with wide swings from 37.6ºC may suggest the diagnosis.

Unless one is dealing with the ovarian vein variant, the pelvic examination is usually unremarkable. In less than 20% of cases can tender, firm wormlike thrombosed veins be identified in the vaginal fornices or in one or both parametrial areas. Not infrequently, a temperature spike occurs within one hour after such an examination (the so-called 'pelvic challenge' test).

No consistent laboratory aids are available for making the diagnosis. The white blood cell count (WBC) is usually elevated and shifted to the left. More than 20000 leukocytes/mm^3 may indicate the concomitant presence of an abscess or conversion of the thrombosed vein into an abscess. Chest X-rays, blood gas determinations, and isotopic lung scans, individually or in combination, are of value only when thromboembolic disease to the lungs is suspected. The rarity with which venograms or intravenous pyelograms contribute to establish the diagnosis precludes their routine utilization. Making a definitive diagnosis usually requires use of one or more of the following: ultrasound, computerized axial tomography (CAT), nuclear magnetic resonance, or radiolabeling of white blood cells.

Blood cultures obtained at the onset of a fever spike may be positive for one or more anaerobic bacteria.

An alternative, less definitive, but clinically important way to make a presumptive diagnosis of thrombophlebitis is with the heparin challenge test (Table 63.1). In this test, the precipitous lysis of fever within 24–36 hours after the attainment of effective anticoagulation is presumptive evidence of pelvic septic thrombophlebitis. Persistence of fever and/or tachycardia after effective anticoagulation has been achieved should suggest an erroneous diagnosis. Heparin will not mask the presence of a concomitant pelvic disease such as an abscess.

THERAPY

Two therapeutic components, antibiotics and heparinization must function simultaneously.

Table 63.2 Computation of heparin loading dose and infusion rate based on body weight

Body weight (kg)	*Loading dose of heparin (units)*	*Infusion rate (units/hr)*
40	3000	700
50	4000	800
60	4500	900
70	5000	1000
80	5500	1100
90	6000	1200

100	6500	1300

Antibiotics

In most cases, patients are already taking antibiotics when septic thrombophlebitis is diagnosed. Complete coverage must be afforded to Categories I and II of the Gainesville Classification. A single antibiotic with appropriate coverage of septic thrombophlebitis is clindamycin. Whatever antibiotic or combination of antibiotics is used must provide coverage for the peptostreptococci and both the penicillin-sensitive and penicillin-resistant Bacteroidaceae and *Prevotella*.

Heparin

The goal of heparinization is to maintain the clotting time at two to three times the normal value four hours after administration. Optimal anticoagulation is obtained with a circulating heparin level of 0.3 U/ml (activated partial thromboplastin time [aPTT] of 1.5–2.5 times control). Several modes of administration are available. Continuous infusion works best, provided that it is properly monitored and given with strict accuracy (Table 63.2). An alternate continuous regimen uses an initial loading dose of 100–150 U/kg with a maximum of 5000 units. Following the loading dose, the initial infusion rate should be 15–25 U/kg/h. An aPTT should be obtained 4 hours after the loading dose and after each dose change. Once a steady state has been achieved, aPTTs should be done daily.

Heparin effects can be reversed rapidly by administration of protamine sulfate in a dose of 1 mg/100 U of administered heparin. No more than 50 mg of protamine should be given over any 15 minute period because protamine itself can cause anticoagulation.

Before administering heparin, a complete blood cell count, platelet count, prothrombin time, aPTT, and urinalysis should be obtained.

How long to continue anticoagulation therapy depends in part on the severity of disease. If prompt lysis of fever occurs and there is no prior evidence of thromboembolic phenomena, heparinization for five to seven days is usually adequate. If evidence of pulmonary emboli can be documented by clinical symptomatology or blood gas determinations, heparinization should continue for three days. For the next two or three days, the dosage should be tapered gradually. Oral anticoagulation should be instituted on the third day of anticoagulation therapy and continued for 30 days or more. Warfarin (Coumadin, Dicoumarol, Panwarfin) has no demonstrable effect on the prothrombin time for at least two or three days. The initial dose of warfarin is 10–15 mg orally. Usual maintenance dose is 5–7 mg/day. Nevertheless, individual dosage schedules may differ widely.

Surgical intervention

Inferior vena cava ligation carries substantial chronic morbidity. Transient devices achieve the same result with less dangerous effects. Operative intervention is reserved for patients who continue to have pulmonary emboli despite adequate anticoagulation.

However, such a procedure does not necessarily preclude continued embolization, which occurs in approximately 7–10% of patients.

Hysterectomy and salpingo-oophorectomy may be necessary if ligneus cellulitis is present. In this setting, the procedure is associated with a high degree of morbidity. The involved tissues bleed freely when excised and hold sutures very poorly.

OVARIAN VEIN VARIANT

Signs and symptoms

Although puerperal ovarian vein thrombophlebitis occurs primarily after delivery, it may also be seen after vaginal or abdominal surgery (Figures 63.1 and 63.2).

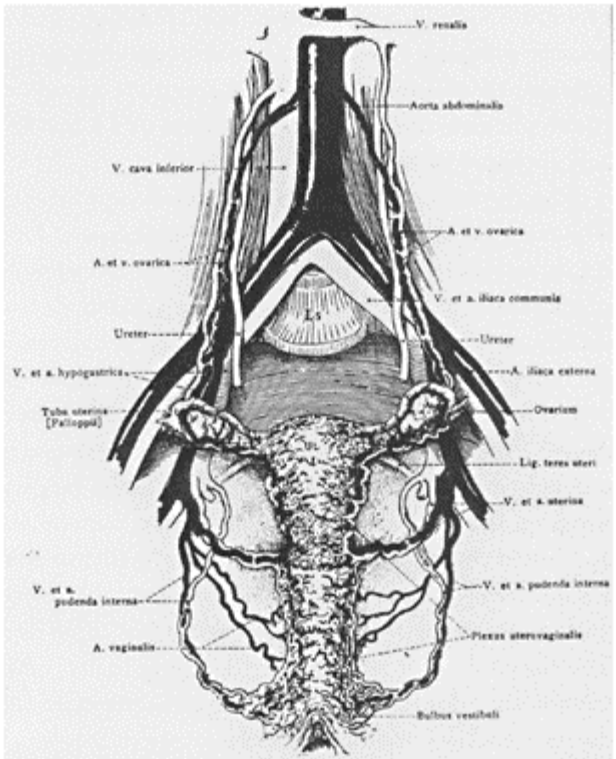

Figure 63.1 Drawing of the inferior vena cava system

The clinical characterization of the syndrome is well described in the collected series of Brown and Munsick. The patient may have fever before feeling any pain; nevertheless, pain is the cardinal symptom in nearly all cases. Initially the pain consists of cramps.

Once the disease has become established, the pain becomes constant and noncolicky. It may vary in intensity from a dull ache to severe and debilitating. The pain may adopt one of several patterns. Most of the time, it resides in the lower abdomen directly over the site of involvement. The clinical presentation is often confused with acute appendicitis. Bilateral pain should alert the physician to the probability of bilateral disease. About 20% of patients may have exclusively costo-vertebral angle pain. Some patients have both abdominal and flank pain.

While the onset of symptoms varies greatly, they usually begin on the second or third postpartum or postoperative day. Fever is often low grade at first. If antimicrobial therapy is delayed, the fever may spike in

Table 63.3 Differential diagnosis for ovarian vein thrombophlebitis

Acute appendicitis
Unilateral right pyelonephritis
Torsion and infarction of right adnexal mass
Ovarian vein thrombophlebitis (bland)
Bowel volvulus

a hectic pattern. When symptoms start, most patients are tachycardic. The pulse rate may be elevated in disproportion to the observed temperature. Some 30–40% of patients have nausea, but vomiting is rare. Segmented ileus manifested by local distention without altered bowel sounds is demonstrable in more than 50% of patients.

While the WBC may be relatively normal, most patients have leukocytosis with a shift to the left. A WBC count of greater than 20000 WBC/mm^3 suggests the possibility of thrombus conversion into an abscess. Demonstration of an elongated, ropelike, exquisitely tender mass confirms the diagnosis. The mass, which may be 2–8 cm in diameter, extends laterally to the lateral margin of the rectus abdominis muscle and cephalad. On physical examination, direct tenderness usually associated with guarding is almost always found at the site of involvement. Mild distention is common, but bowel sounds are usually normal. Bimanual examination is likely to reveal some tenderness and possible induration involving the parametrium and broad ligament of the site of involvement. Table 63.3 presents considerations for the differential diagnosis. CT can be indicated not only for diagnosis confirmation but also to determine the extent of ovarian vein thrombosis.

Management

Therapy for ovarian vein thrombophlebitis is the same as for septic thrombophlebitis. When the former converts into an abscess (a rare occurrence), the thrombosed vein must be surgically removed. Witlin *et al.* reported a series in patients with ovarian vein thrombosis. Patients responded an average of 4.7±2.1 days after heparin therapy was started. Unfortunately, the mean

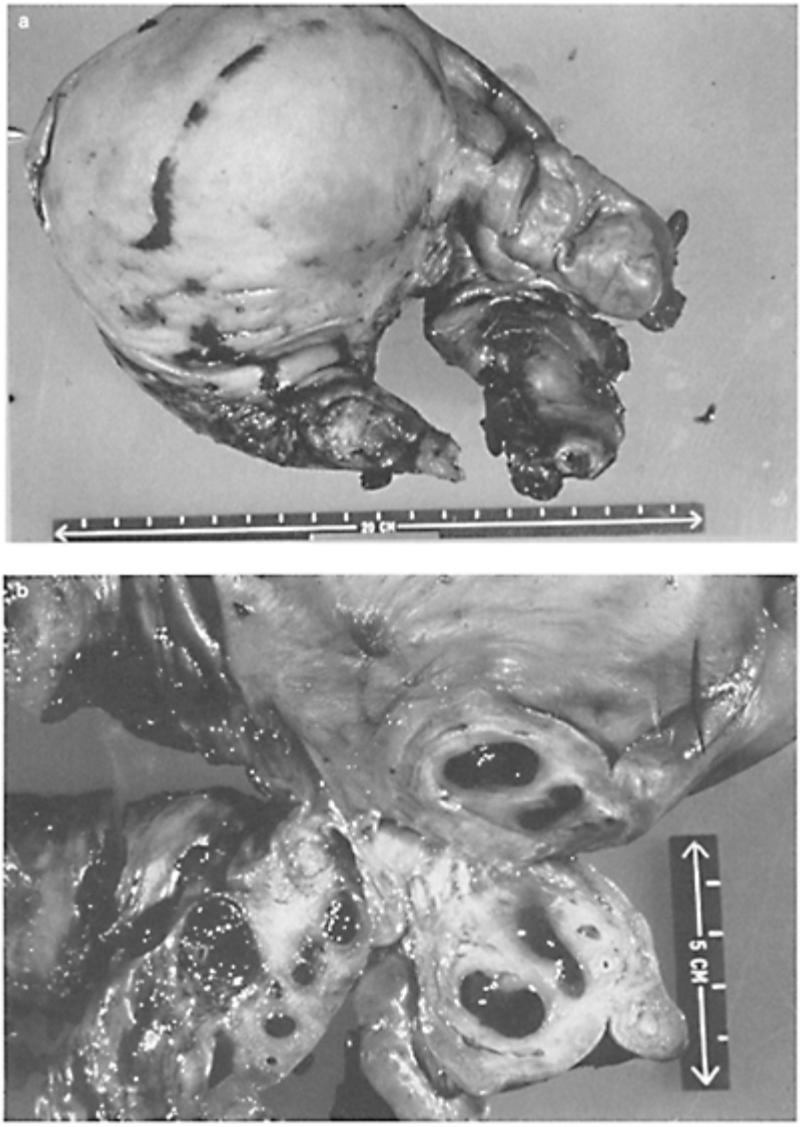

Figure 63.2 (a) Mass created by a right ovarian vein thrombophlebitis. (b) Close-up of section demonstrating thrombus of the ovarian vein and collateral circulation.

time of febrile morbidity to institution of therapy was 5.5±1.9 days. The longer a process has functioned, the longer the time from effective anticoagulation to defervescence.

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Infectious complications associated with legal termination of pregnancy

The legal termination of pregnancy has had a dramatic impact on the severe infectious morbidity associated with criminal abortion, but, in so doing, has introduced its own spectrum of infectious morbidity. The severity of infectious complications increases with gestational age because of the mode of termination of pregnancy which must be utilized. The primary contributing factors are those of omission or commission. The principal error of omission is the failure to monitor the patient for occult infection due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis* prior to the operative procedure. The errors of commission involve primarily technical errors—failure to completely evacuate the uterus or to ensure adequate hemostasis. The infectious morbidity observed is partially dependent on the trimester in which the operative procedure is performed (Table 64.1).

TRIMESTER I (1-14 WEEKS)

Completed abortion/exogenous pathogens

Acute endometritis/salpingitis/peritonitis due to *N. gonorrhoeae* or the group A or B beta-hemolytic streptococci may occur. In these instances, mechanical disruption of pregnancy has provided the portal of infection. Superinfection by class I and II anaerobes will ultimately occur.

Gonococcal septicemia or arthritis-cutaneous syndrome may ensue. Surgical disruption of mucosal barriers creates not just a portal of infection but also access to the intravascular compartment.

Infection due to *C. trachomatis* may be subtler in clinical presentation, with symptoms so mild, i.e. vaginal discharge, continued spotting, minimal abdominal

Table 64.1 Infectious morbidity associated with uterine curettage

(1) Superimposed due to the presence of exogenous virulent pathogen at the operative site, i.e. groups A, C and G beta-hemolytic streptococci, *Neisseria gonorrhoeae, Haemophilus influenzae* or *Chlamydia trachomatis*

(2) Associated with retained products of conception

(3) Surgical trauma to the uterus

A Recognized surgical trauma to uterus

	(i)	Midline presentation
	(ii)	Lateral uterine perforation
B	Unrecognized surgical trauma to uterus	

discomfort, that the patient may not seek medical care. Too often, the result is fallopian tube damage, which compromises the patient's future obstetrical potential.

Septic incomplete abortion

The patient presents early, within 24–48 hours of the operative procedure, because of crampy abdominal pain. In addition to simple technical errors, frequently anatomical variations of the uterus contribute to incomplete septic abortion, e.g. septated uteri favor retained products of conception.

Lateral wall perforation/cervical tear with extension

The uterine artery bifurcates approximately 3.8 cm from the endocervix into an ascending and descending (cervical) branch. If an endocervical tear extends to and disrupts this branch of the uterine artery, significant bleeding may occur into the broad ligament with ensuing hematoma formation. Contamination or seeding from the vaginal flora will ultimately lead to abscess formation. The first evidence of febrile morbidity manifests approximately 36 hours after operative intervention.

Central fundal perforation

The position of the uterus may predispose to central perforation at the fundus. This probably occurs more frequently than clinically appreciated. Usually fundal perforation is benign because it is sealed by the omentum or small bowel; however, if Cesarean section is required at a later date, the operation is likely to be technically more difficult. If the suction curette has devitalized adjacent bowel, severe delayed infectious morbidity may ensue as a consequence of perforation and peritonitis or abscess formation. If the uterus is perforated with a suction curette and omental fat or bowel is observed, a laparotomy must be done to identify or exclude concomitant bowel injury.

TRIMESTER II (14–20 WEEKS)

The hysterotomy incision is comparable to that of classical Cesarean section in which serum and blood can leak into the peritoneal cavity. The infectious complications are the same as those for Cesarean section:

(1) endometritis/peritonitis/cellulitis septic thrombophlebitis;
(2) pyometra (secondary inflammatory closure of the endocervix);
(3) uterine-wall hematoma with abscess formation; and
(4) abdominal wound infection.

If a low vertical incision is used and the operative site is not covered with bladder and chromic gut sutures are used, small bowel obstruction has occurred in rare instances.

The use of PGF2 alpha has markedly diminished in recent years. The triad of unacceptable patient symptomatology prior to evacuation of the uterus, the delivery of a live fetus, and the frequent problems of a retained placenta, which requires operative intervention, has lessened physician enthusiasm for this procedure.

Vaginal evacuation of the unwanted pregnancy of 14–24 weeks is associated with fewer problems than alternative methods, if a few caveats are observed. The physician doing the procedure must be both skilled and experienced. He or she must have access to an operating room with a competent anesthesiologist. The operation area must have competent assistants available, who do not disapprove of the procedure, and the necessary equipment needed to perform the procedures. The procedure requires the preoperative insertion of the laminaria in the cervix to permit slow dilation over time and the availability of instruments to reduce the size of fetal parts so evacuation will be complete.

Infectious problems can occur. They can be due to the presence of virulent exogenous pathogens, such as *Streptococcus pneumoniae,* the group A streptococci, *N. gonorrhoeae* or *C. trachomatis*. Many of these pathogens can be preoperatively identified and eliminated by appropriate testing.

Most infectious problems are due to either immediate tissue damage, uterus perforation with bleeding and subsequent infection, or slowly evolving infection emanating from retained products of conception.

PATHOGENESIS

Exogenous virulent pathogens

Infection due to exogenous virulent pathogens usually occurs within 8 hours or less of the procedure. If due to the group A, C or G beta-hemolytic streptococci, the patients get very sick rapidly. The oral temperature is usually greater than 39.6ºC. Pelvic examination reveals marked tenderness with little evidence of inflammatory exudate. Gram stains of the uterine swab reveal an abundance of Gram-positive cocci in chains and few, if any, concomitant bacteria. Screening for *N. gonorrhoeae* in high risk populations is advisable. Screening for *C. trachomatis* should be done for all women. If the endocervical culture is positive at the time of curettage, the infection rate for women undergoing operative termination of pregnancy increases threefold. Approximately 15% of women harboring the gonococcus at the endocervix develop postabortal infection. Some centers have addressed this problem by utilizing antibiotic prophylaxis for all women undergoing curettage. Such a policy does obviate the need for screening for *N. gonorrhoeae* in high risk populations. The gonococcus has epidemiological significance and potential adverse consequences which extend beyond the patient. When disease is due to a superimposed virulent pathogen concomitantly present at the operative site, the initial drug of choice is a betalactamase-resistant third-generation cephalosporin such as ceftizoxime or cefotamine. The rationale for selective use of these antibiotics over a semi-synthetic penicillin or a new generation tetracycline are:

(1) that very real homage has to be paid to penicillinase-producing strains of *N. gonorrhoeae;* and
(2) that the tetracyclines are suboptimal antibiotics for both aerobic and anaerobic streptococci.

Antibiotic therapy should be continued until the following sought-for therapeutic response is attained:

(1) no temperature equal to or greater than 37.6ºC for 24 hours;
(2) absence of local physical findings; and
(3) a normal white blood cell count.

Once these parameters have been attained, parenteral drug therapy is discontinued and the patient is discharged on per oral doxycycline 100 mg b.i.d. x 7 days, or given azithromycin one gram bolus dose. One in every three women with gonococcal infection is concomitantly infected with *C. trachomatis*. If disease is due to a beta-hemolytic streptococcus, a simple 4- to 5-day course (500 mg t.i.d.) of per oral amoxicillin suffices and even this probably represents overkill. Even when the gonococcus is present, it is imperative to document the absence of retained products of conception.

If the patient is polymerase chain reaction positive for *C. trachomatis,* she should receive a 10–14 day course of doxycycline, orally.

Retained products of conception

The diagnosis of retained products of conception is inferred by the detection of a foul-smelling discharge. The onset of disease is usually delayed for several days. A vaginal ultrasound is helpful in detecting retained secundines within the uterine cavity. Gram stain of the endometrium reveals mixed flora amidst white blood cells. Most patients with postabortion infection due to retained products of conception respond readily to combined medical/surgical therapy. The patient is placed on a combination of antibiotics. A number of parenteral antibiotic combinations have been successful:

(1) penicillin 4–8 million units/24 hours and gentamicin 3 mg/kg of body weight/24 hours;
(2) ampicillin/sulbactum 6.0 g/24 hours;
(3) gentamicin 3 mg/kg of body weight/24 hours and clindamycin 2400–2700 mg/24 hours.

A curettage is performed within 4–8 hours after admission, irrespective of whether or not the patient has become afebrile from systemic antibiotic therapy. The presence of signs or symptoms following combined therapy should question the validity of the initial diagnosis. The need for continued antibiotic therapy once the anticipated therapeutic response has been attained is questionable. The use of ampicillin 500 mg q.i.d.× 4–5 days has been used for potential medical-legal rather than serious therapeutic considerations. Once the previously defined therapeutic end titration points are achieved, no further antibiotic treatment is necessary. Longer courses of antibiotic administration increase the chance of an adverse drug reaction.

Unrecognized surgical trauma

Midline perforations of the uterus with the uterine sound in the absence of excessive bleeding in a patient whose vital signs are stable necessitates little more than careful observation. Many physicians will administer antibiotics in this clinical setting. No valid well-controlled studies support or refute the utility of prophylactic antibiotics. If antibiotics are given, the course of therapy should be relatively short. Duration of administration should be governed by temperature curve, vital signs and physical findings. The presence of unstable vital signs or excessive bleeding warrants immediate operative evaluation. Recognized lateral uterine perforation mandates immediate laparotomy. The patient must be carefully evaluated for damage to the small or large bowel. Prophylactic administration of cefoxitin, if small bowel damage is identified, or metronidazole, if large bowel damage is identified, appears warranted on theoretical grounds. Patients presenting with unrecognized uterine damage at the time of curettage also require operative evaluation. The majority of these patients will be found to have an infected extrauterine hematoma. A rare patient will have an adnexal abscess. The use of two-drug therapy with category designation in Categories I and II is indicated. Duration of therapy postoperatively is dictated by clinical parameters.

MANAGEMENT OF THE PATIENT WITH DELAYED POSTABORTAL INFECTION

The principal differential is distinguishing those patients with retained products of conception from those with unrecognized surgical trauma to the uterus. In both situations the onset of signs and symptoms of disease is delayed. Both subsets of patients present with fever and tender uterus. The presence of foul-smelling discharge should strongly suggest the possibility of retained products of conception, which can be confirmed by vaginal ultrasound examination. The presence of a tender pelvic mass contiguous to the uterus and an unexplained drop in the hematocrit argues for unrecognized surgical trauma to the uterus. Peritoneal signs (rebound tenderness) are rarely associated with retained products of conception unless infection due to the group A beta-hemolytic streptococci is present. Gram stain of the endometrium or cul-de-sac aspirate can readily sustain or negate this clinical possibility.

If peritoneal signs are present or the patient’s condition worsens, a roentgenogram of the pelvis or a CAT scan is indicated. The presence of a gas pattern in the uterine wall, the pelvis or a local ileus are indications for surgical intervention.

If peritoneal signs are present, baseline biopsy cultures of the endometrium and aspiration culture of the cul-de-sac are recommended. Blood cultures should be done in all patients who:

(1) have advanced disease;
(2) have peritoneal signs; and
(3) have a prior history of rigors.

A complete blood count and differential are necessary baselines. The demonstration of asymptomatic bacteriuria warrants the concomitant use of an aminoglycoside, a third generation cephalosporin or a fluoroquinolone with optimal anaerobic coverage. The

persistence of fever for more than 36 hours after triple therapy and uterine evacuation can be an indication for exploratory laparotomy. Metronidazole should be added to the ongoing antibiotic regimen. If fever persists, laparotomy is indicated.

If the diagnosis is that of surgical trauma, definitive therapy requires surgical intervention under antibiotic coverage. Operative vaginal termination of late pregnancy carries with it the risk of endomyometritis. If tubal ligation is done with hysterotomy, the incidence of infectious complications may be increased.

IMPACT OF THE ABORTION-ASSOCIATED INFECTION ON SUBSEQUENT FERTILITY

The common conception that subsequent fertility is significantly impaired by prior legal termination of pregnancy is difficult to substantiate on statistical grounds. When the issue of ectopic pregnancy in subsequent pregnancies has been looked at, the risk of ectopic pregnancies could not be related to abortion procedures, use of laminara, number of prior induced abortions, or the length of gestation at time of abortion. Where an association did exist was between the presence of post-abortion infection or retained secundines and ectopic pregnancies. Women with these complications have a five-fold increased risk of an ectopic pregnancy over those females without these complications within the induced abortion cohort group.

Table 64.2 Proposed criteria for the prophylactic use of antibiotics in gravidas undergoing voluntary termination of pregnancy*

I.	Prior documentation of salpingitis or infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*
II.	Multiple sexual partners
III.	Sexual consort with multiple secondary sexual partners
IV.	Gravida with mucopurulent cervicitis or a significant vaginal discharge

*These patients should be evaluated for gonococcal and chlamydial infections. If documented, appropriate documentation of cure and treament of sexual consorts is advocated

LEGAL TERMINATION OF PREGNANCY

In an analysis of febrile morbidity involving 26 332 women who underwent suction curettage abortion. Park *et al.* demonstrated a 3.4% incidence of infectious complications. Using a multivariate analysis, prophylactic antibiotics proved to be the most protective factor. Women who received prophylactic antibiotics and women who had previous deliveries were less likely to have febrile complications. More recently Sawaya *et al.* performed a literature search of all studies published from January 1966 to September 1, 1994, using MEDLINE, and they manually searched bibliographies of published articles. Using meta-analytic techniques on 12 studies, the authors demonstrated a substantial

protective effect of antibiotics in all subgroups of women undergoing therapeutic abortion, even women in lowrisk groups. They calculated that routine use of periabortal antibiotics in the United States may prevent up to half of all cases of postabortal infections. In the absence of specific contraindications, the cost of prophylaxis may be justified in high-risk populations (Table 64.2). Immediate prophylaxis can be achieved readily with any antibiotic with good Category I coverage (Gainesville Classification).

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65
Septic shock

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Shock is a pathological state in which the body's blood pressure is lowered to such a degree that tissue perfusion is limited. If this condition proceeds unaltered, cellular hypoxia and eventually death will occur. There are different types of shock: cardiogenic shock, related to pump failure; hemorrhagic or hypovolemic shock, related to acute blood loss, and neurogenic shock, related to loss of sympathetic control of vessel resistance. Septic shock has an infectious focus as its inciting event. This type of shock can have components of all the other types of shock, especially cardiogenic and hypovolemic. It occurs in the presence of severe sepsis, when the mechanisms of a systemic inflammatory response to a microbial invasion go astray. In the case of severe septic shock, the release of numerous pro-inflammatory cytokines contributes to multiple organ dysfunctions, and sometimes to death. In the United States, the incidence of septic shock is increasing with a greater proportion of cases due to Gram-positive aerobic organisms. This is probably related to the increasing age of our population, an ever-increasing number of HIV positive patients, and increasing numbers of invasive therapies (organ transplant, bone marrow transplant) that utilize immunosuppressive treatments. In contrast to this overall trend, the number of cases of septic shock in Obstetrics-Gynecology is probably less than in the 1960s. Improved antibiotic treatments targeting Gram-negative anaerobes have contributed by lessening the numbers of patients with a ruptured tubo-ovarian abscess. Social changes have been the bigger contributor to lessening numbers of patients with septic shock. Legal terminations of unwanted pregnancies have nearly eliminated the desperate 'back alley' attempts to eliminate pregnancies of the 1950s and 60s. In those days, women with pregnancies beyond twelve weeks would be subjected to the insertion or injection of tissue damaging substances in often-unclean circumstances. Hopefully, those dark days will not be revisited in the United States.

SEPTIC SHOCK IN OBSTETRICS

Despite the high incidence of localized infections in obstetric patients, bacteremic obstetric patients rarely proceed to develop such complications as severe sepsis or septic shock. Only about 4% of pregnant patients with bacteremia will develop septic shock.

The mortality from septic shock in obstetric patients is only 0–3%, compared to the high rate of mortality in other patient populations, which can be as high as 25–81 %. The lower mortality rate in obstetric patients is due to:

(1) a younger age group;
(2) the transient nature of the bacteremia;
(3) the organisms involved;
(4) the primary site of infection (the pelvis) is more responsive to medical and operative therapy; and

(5) the lack of any underlying disease state.

Despite its apparent rarity, septic shock still constitutes a major cause of obstetric maternal and gynecologic deaths. In obstetric and gynecologic patients, the principal entities that predispose to septic shock are post-cesarean endomyometritis, infected abortion, acute pyelonephritis, acute chorioamnionitis, posthysterectomy adnexal abscesses, pelvic or tubo-ovarian abscesses, and synergistic bacterial infections that can result in widespread tissue death.

Microbiology

The microorganisms responsible for sepsis usually derive from the patient's endogenous microbial flora, but on occasion are acquired during hospitalization. The principal pathogens responsible for septic shock in obstetric and gynecologic patients are part of the normal flora of the lower genital tract. Gram-negative bacteria are responsible for the majority of these infections. The most commonly implicated organisms are Gram-negative aerobes, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter*, *Klebsiella*, and *Pseudomonas*, but recently there has been an increase in the incidence of sepsis due to Gram-positive organisms. Septic shock in a woman with an infected abortion with *Clostridium perfringens* is fortunately an event that has been nearly eliminated in this age of early legal termination of unwanted pregnancies.

Pathophysiology

The human female host has an immediate response to any bacterial invasion. The innate immune system of humans has been highly conserved throughout evolution to recognize specific pathogen associated molecular patterns on the surface of infectious microorganisms. Toll family pattern recognition receptors are present on epithelial cells at mucosal surfaces as well as on macrophages and dendritic cells. They are primed to recognize molecular patterns of potentially dangerous agents including endotoxin, bacterial pathogen DNA, peptidoglycans, and mycoloic acid. For example, one toll like receptor, TLR4, has a receptor specificity for the lipopolysaccharide of Gram-negative aerobic bacteria. The activation of these pattern recognition receptors results in the synthesis and release of tumor necrosis factor (TNF), interleukin 6, and interleukin 8. These pro-inflammatory cytokines in turn activate leukocytes. This is all part of a multi-faceted host defense mechanism against infection.

Parallel to this innate immune response, the complement system recognizes and responds to pathogen associated molecular patterns. This results in the activation and release of the complement cascade. A wide range of complement factors bind to receptors on a variety of cells. This has the potential for both good and bad results. On the plus side, activation of these receptors results in leukocyte chemotaxis, release of granule bound enzymes and cytokines, activation of NADPH oxidase, and enhancement of vascular permeability. All of these responses should aid the host in mounting a defense against invasive bacterial pathogens. Unfortunately, inflammatory cytokines also have the ability to harm the host. There are many clinical examples. For the gynecologist, the relative absence of the proinflammatory cytokine blocker, interleukin 1 receptor antagonist (IL1-ra), in women with a specific gene polymorphism leads to a chronic

inflammatory vulvar syndrome, vulvar vestibulitis. It has also been postulated that excessive production of the complement C5a in septic patients could paradoxically reduce leukocyte function. These observations pose many future therapeutic possibilities. In addition to antibiotic chemotherapy to decrease the number of pathogens and operative therapy to remove the site of infection in the pelvis, new medications that block the C5a receptor could be part of the future care of women with sepsis.

Endotoxin can activate Hageman factor (XII), which, in turn, initiates the intrinsic clotting cascade. Hageman factor also directly activates factor VII, stimulating the extrinsic coagulation pathway. Unleashing the coagulation system leads to concurrent activation of the fibrinolytic system. Plasmin, the active component of the latter system, then acts upon Hageman factor to produce prekallikrein activators. These substances convert prekallikrein to kallikrein, which in turn causes conversion of plasminogen to plasmin and also directly activates Hageman factor. This enhanced coagulation and accelerated fibrinolysis sets the stage for the phenomenon of disseminated intravascular coagulation. Another major effect of kallikrein activation is the production of a variety of inflammatory mediators such as hydrogen peroxide, free radicals, and bradykinin. These substances cause intense inflammatory injury to vital organs.

In addition, as sepsis evolves, intense activation of the sympathetic nervous system is manifested by increased catecholamine release from peripheral nerves and the adrenal medulla. This sympathetic discharge causes generalized vasoconstriction in virtually every vascular bed. The vasoconstriction is intensified by the local effects of prostaglandins released from injured endothelial tissue.

The most serious effect of generalized vasoconstriction is decreased perfusion of vital organs, resulting in localized tissue hypoxia and acidosis. As acidosis evolves, there is a major change in circulatory hemodynamics, characterized by relaxation of smooth muscle in the wall of arterioles and constriction of smooth muscle in the wall of venules. This process leads to extensive pooling in most capillary beds, increased by hydrostatic pressure, and transudation of intravascular fluid into the extravascular space. Generalized capillary pooling causes a marked decrease in effective circulating blood volume and corresponding decreases in venous return, cardiac output, and systemic blood pressure.

In addition to decreased venous return, at least three other factors contribute to impaired myocardial contractility. First, circulating beta endorphins are increased. These peptides are released from the pituitary gland along with adrenocorticotropic hormone (ACTH) in response to stress. Their principal hemodynamic effects are to lower blood pressure and decrease heart rate. Second, endotoxin itself has a direct depressant effect on myocardial contractility. Third, several studies have identified the presence of a specific shock factor, termed myocardial depressant factor (MDF), which apparently is released from the ischemic pancreas during evolution of the shock state. MDF gradually accumulates in the plasma of shocked animals in direct proportion to the severity of splanchnic ischemia. The most important biologic effect of MDF is depression of myocardial contractility. It also enhances vasoconstriction within splanchnic blood vessels, thus accelerating its own production, and directly depresses the phagocytic capacity of the reticuloendothelial system, resulting in impaired clearance of lysosomal enzymes and MDF from the circulation.

As cardiac output initially begins to fall, local regulatory mechanisms attempt to preserve perfusion of the coronary and cerebral vascular beds. However, if the

hemodynamic changes precipitated by septicemia are not corrected, there is progressive diminution in cardiac output and, ultimately, compromise of both coronary and cerebral blood flow. Maintenance of cardiac output correlates directly with ultimate survival.

Respiratory failure

Endotoxemia causes profound derangements in the host's pulmonary system. Endotoxin directly damages the endothelium of the pulmonary vasculature. As disruption of capillaries occurs, platelets adhere to fragments of exposed collagen. Release of platelet factor 3 activates the intrinsic coagulation cascade, resulting in microembolization and stasis of blood flow in the pulmonary microcirculation. Prostaglandins are released from platelets and injured endothelium and cause pulmonary vasoconstriction. The net effect of these processes is impairment of pulmonary perfusion, ischemia, and progressive injury to the vascular endothelium. Cerebral ischemia resulting from hypotension intensifies pulmonary vasoconstriction.

Endothelial injury leads to continued activation of the complement cascade. Increased serum concentration of C5a is a useful predictor of subsequent development of adult respiratory distress syndrome (ARDS). Complement activation causes damage to the lung by enhancing leukocyte migration into the pulmonary parenchyma. Leukocytes, in turn, release several inflammatory mediators which cause profound injury to the vasculature and parenchyma of the lung. The activity of the proteolytic enzyme, elastase, is increased in bronchoalveolar lavage fluid obtained from patients with ARDS.

Continued inflammation results in increased capillary permeability, transudation of protein-rich fluid into the interstitium and alveolus, and destruction of surfactant. The functional consequences of these events are extensive atelectasis, perfusion-ventilation imbalance, decreased compliance, interstitial and intra-alveolar edema, severe hypoxemia and, ultimately, respiratory failure.

Other effects of endotoxin

Endotoxin adheres to the cell membrane of circulating leukocytes, causing these cells to be removed from the circulation by reticuloendothelial cells. Therefore, neutropenia may be present early in the course of septic shock. As cell-mediated immunologic defenses are mobilized, however, rebound leukocytosis usually ensues except in immunosuppressed patients.

Endotoxin exerts a prominent effect on the temperature-regulating center of the hypothalamus. In the early phase of sepsis, the hypothalamic center may be depressed, and hypothermia may be present. As shock evolves, however, the principal effect of endotoxin is activation of the hypothalamic center and elevation of body temperature, an effect mediated by release of endogenous pyrogen from host leukocytes.

The end point of septic shock is a profound hypodynamic state, characterized by intractable hypotension and severe metabolic acidosis. Clinically, this is manifested by coma, complete vasomotor collapse and multiorgan failure.

CLINICAL MANIFESTATIONS

Restlessness, anxiety, and disorientation are among the earliest manifestations of septic shock. Another early physical sign is temperature instability. In the initial stages of septic shock, patients frequently are hypothermic; as sepsis progresses, patients typically become hyperthermic.

The most prominent pathophysiologic changes are those affecting the cardiovascular system. In the majority of patients, a hyperdynamic state is present initially. Cardiac output and myocardial oxygen consumption by peripheral tissues is increased, and total peripheral resistance is decreased. As shock progresses, intense, generalized vasoconstriction occurs. Accordingly, there is a transition to a hypodynamic cardiac state characterized by a decrease in cardiac output, systemic blood pressure, and perfusion pressure. Diminished tissue perfusion, in turn, leads to myocardial dysfunction, which is manifested by tachycardia, arrhythmia, myocardial ischemia, and ultimately, biventricular failure.

Twenty-five to 50% of patients with septic shock develop ARDS. The usual clinical signs of this disorder are tachypnea, dyspnea, stridor, and central cyanosis. Examination of the chest demonstrates dullness to percussion, decreased tactile and vocal fremitus, diminished breath sounds, and prominent rales throughout both lung fields.

Examination of the patient is important in establishing the primary site of infection and in identifying other organ systems compromised by the shock state. In obstetric-gynecologic patients, a careful search for evidence of severe gastrointestinal disease should be performed. In nearly all cases, our focus is on renal parenchymal disorders such as acute pyelonephritis or perinephric abscess. Post-operation septicemia also may result from surgical complications such as ureteral injury, wound infection, necrotizing fasciitis, evisceration, undetected bowel damage at the time of operation, or intra-abdominal abscess formations and rupture. Palpation of enlarged and/or tender pelvic viscera or a pelvic mass suggests the possibility of a pelvic abscess. Depending upon the primary site of infection and the severity of the evolving septicemia, other clinical manifestations of septic shock may include hematuria, pyuria, oliguria, jaundice, nausea, and vomiting. Spontaneous hemorrhage from the gastrointestinal or genitourinary tracts or bleeding from venipuncture sites can indicate the presence of coagulopathy.

DIAGNOSIS

Disorders to be considered in the differential diagnosis of septic shock include cardiogenic and hypovolemic shock, pulmonary embolism, amniotic fluid embolism, cardiac tamponade, aortic dissection, hemorrhagic pancreatitis, and diabetic ketoacidosis. Distinction between septic shock and these entities usually can be made on the basis of history, physical examination, and the selected laboratory tests outlined below.

Hemodynamic monitoring is of critical importance in establishing the diagnosis of septic shock. Electrocardiography should be performed to rule out myocardial ischemia

and to detect arrhythmias. Echocardiography will detect valvular abnormalities in patients who have septicemia due to endocarditis.

In the initial stages of septic shock, the white blood cell count may be decreased due to sequestration of neutrophils in the spleen. Neutropenia is usually followed by a prominent leukocytosis, however. The hematocrit may be decreased if acute blood loss accompanies sepsis. Alternatively, the hematocrit may be increased as a result of decreased circulating plasma volume.

A variety of coagulation abnormalities may occur in septic shock, including thrombocytopenia, decreased concentrations of factor XII and antithrombin III, and an increased concentration of fibrin degradation products (FDP). Fibrinogen concentrations may be either increased or decreased, depending upon the balance between acute-phase synthesis and consumption of this molecule. Persistence of coagulation abnormalities, particularly thrombocytopenia, is an extremely poor prognostic sign.

Early in the evolution of septic shock, respiratory alkalosis may be present as a result of hyperventilation. Respiratory alkalosis typically is followed by a profound metabolic acidosis, however. Lactate is the major organic acid responsible for the metabolic acidosis. The severity of the patient's circulatory dysfunction and the ultimate prognosis for survival correlate directly with the serum concentration of lactate.

In septic patients with concurrent ARDS, respiratory acidosis may contribute to the systemic acidosis. This state of mixed metabolic respiratory acidosis is manifested by decreased arterial pH, decreased serum bicarbonate, and increased arterial pCO_2. Hyperkalemia may develop as intracellular potassium migrates from the cell in exchange for hydrogen ions.

Renal function may be altered in the patient who has septic shock. It is important to have a constant monitor of urine output with an indwelling catheter. As renal blood flow decreases, output diminishes and then ceases. Creatinine and inulin clearance decrease. Serum concentrations of blood urea nitrogen, creatinine, and uric acid then increase.

Abnormalities of liver function also are common in patients with septic shock. These include clinical jaundice and biochemical alterations such as elevated bilirubin, alkaline phosphatase, and transaminase concentrations.

Microbiologic cultures are essential to establish the diagnosis of sepsis and to determine the primary site of infection. A sample of urine should be obtained from the indwelling catheter for microscopic examination and culture. Sputum culture and Gram stain are indicated in patients who have pneumonia. Aerobic and anaerobic blood cultures should be collected. In patients receiving parenteral hyperalimentation or immunosuppressive drugs, blood specimens also should be cultured for fungal organisms. When it is possible, aerobic and anaerobic cultures of operative site, wound, or abscess contents should be obtained.

Chest X-ray is indicated to detect pneumonia, septic pulmonary emboli, pulmonary edema, and ARDS. Immediate recognition of the last disorder is essential, since it so adversely affects the patient's ultimate prognosis. Abdominal radiographs can be helpful in diagnosing the septic patient with acute peritonitis. They can diagnose intestinal obstruction or perforated viscus. Computerized tomography, magnetic resonance imaging (MRI) or ultrasonography may aid in delineating a pelvic or abdominal abscess and urinary tract stones or damages.

MANAGEMENT

Correction of hemodynamic derangements

Once the diagnosis of septic shock is established, a bladder catheter should be inserted to monitor urine output. Two large-bore intravenous catheters should be inserted to administer fluids and medications. Intensive therapy doctors should be consulted to place a central line. The most important thing to do is to determine if immediate operative intervention is needed. Fluid resuscitation should be initiated while physiologic monitors are being placed. If the patient has experienced acute blood loss, administration of packed red blood cells may be required. In the absence of blood loss, plasma deficits should be corrected by infusion of isotonic crystalloids such as normal saline or lactated Ringer's solution or colloid solutions such as albumin or plasmanate. Initial fluid replacement should be in small increments of 150 to 200 ml infused over 10 minutes. Adjustments in the rate of infusion should be made on the basis of evaluation of blood pressure, pulse, jugular venous pressure, and urine output.

Treatment of infection

Antibiotic therapy should be initiated after cultures have been obtained. Although it is not the only acceptable regimen, the antibiotic combination of cefotoxin, aminoglycoside, and metronidazole provides effective coverage for virtually all potential genital tract pathogens.

Elimination of the source of infection frequently requires surgery, for example to drain an abdominopelvic abscess, to remove infected products of conception, to extirpate grossly contaminated pelvic organs, or to debride devitalized subcutaneous and fascial tissue in the abdominal wall. Surgical intervention is, in fact, the single most important step in stabilization of the critically ill patient. Definitive surgical therapy should not be delayed simply because the patient's blood pressure and tissue perfusion respond initially to fluid resuscitation.

The management of the gravid patient with septic shock due to chorioamnionitis presents a particularly difficult problem for the obstetrician. The maternal and fetal prognosis in chorioamnionitis has improved remarkably in recent years. This is due to early diagnosis and aggressive treatment with newer antibiotics. The maternal and fetal prognosis may not be so favorable, however, when chorioamnionitis and septic shock coexist. Prompt delivery of the fetus, by Cesarean section if necessary, is indicated if the parturient's cardiovascular dysfunction does not improve with the measures outlined above and probably it should be done in view of the increased risk of cerebral palsy in the infants of women with chorioamnionitis.

With the wide range of inflammatory immune responses to sepsis, one strategic view of therapy is based upon the belief that the patient is more in danger from this host response than from the infecting microorganisms. A wide series of interventions to block this overwhelming and dangerous inflammatory response have been tried with limited success. This suggests that our knowledge of the complex, inter-related host response is still incomplete, There are many examples. Steroids have been widely used, but without evidence of benefit in all of the large-scale trials that have been mounted. At times, the

treatment intervention has been counter-productive. For example, one study of treatment of septic shock with TNF receptor: Fc fusion protein did not reduce mortality and at higher doses appeared to be associated with increased mortality. There are elements of hope. Treatment with recombinant human activated protein C reduced mortality in patients with severe sepsis although it was associated with an increased risk of bleeding. This is an ongoing story of clinical research that has not yet reached fruition.

Support of the respiratory system

Twenty-five to 50% of patients with septic shock develop ARDS. The mortality rate in septic shock complicated by respiratory failure may be as high as 90%, almost twice that in septic shock without ARDS. A major objective in management of the critically ill patient, therefore, is prevention of respiratory failure. Immediate resuscitative measures should include administration of oxygen by nasal cannula or face mask. Arterial blood gases should be monitored frequently to detect early onset of respiratory failure. Excessive fluid replacement should be avoided. Most importantly, the patient should be managed with mechanical ventilation at the earliest manifestation of decreased pulmonary compliance, thereby preventing irreversible damage to the pulmonary vasculature from sustained hypoxia.

Additional supportive measures

It is essential to prevent wide fluctuations in the patient's temperature, since thermal instability may aggravate existing cardiovascular dysfunction. Coagulation abnormalities should be identified promptly and corrected by administration of cryoprecipitate, fresh frozen plasma, fresh whole blood, or platelets. Only in unusual circumstances should it be necessary to consider use of heparin for management of a consumption coagulopathy. In immunosuppressed patients, especially those with infections due to *Pseudomonas* organisms, transfusion of compatible white blood cells may be indicated. A study of neutropenic patients with Gram-negative bacteremia has documented improved survival in individuals who received white cell transfusions in addition to appropriate antimicrobial therapy

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66a
Appendicitis in pregnancy

Appendicitis is the most common cause of an acute abdomen pain in women. Its incidence in women of childbearing age is not altered by pregnancy. The disease appears to be more common in the first two trimesters than in the third. The clinical manifestations of acute appendicitis in pregnancy are more protean owing to the change in both the position and axis of the appendix during gestation (Figure 66.1).

Baer *et al.* have demonstrated a gradual shifting in position of the base of the appendix from its normal low-lying position near the iliac fossa to one somewhat above the iliac crest near term. After the seventh month 88% of all gravidas have their appendix above the iliac crest. The long axis of the appendix also changes from its normal downward and inward direction, first to a horizontal position which points medially, and finally to a vertical position curving around the fundus of the uterus. As a consequence of this gradual outward and upward displacement of the appendix by the growing uterus, the classic localization at McBurney's point is altered.

Were it not for the changing position of the appendix, the symptoms of acute appendicitis in pregnancy would be comparable to those in the non-pregnant female. In the early months of pregnancy the diagnosis of appendicitis is readily established: the classic combination of a history of right lower quadrant pain, nausea, vomiting, and fever, together with the point of tenderness over McBurney's point, is presumptive evidence of the diagnosis.

In pregnancy, nausea *per se* is of limited diagnostic significance unless accompanied by other signs and symptoms suggesting appendicitis. The abdominal spasm that is typical in the non-pregnant patient is less pronounced owing to the presumed laxity of the abdominal muscles. The presence of rectal tenderness or the presence of a psoas sign are valuable diagnostic adjuncts.

As gestation progresses, the differential diagnosis is augmented, particularly when the appendix is to be found in the region of the liver or along the right costal margin. It is in these situations that cholecystitis and right-sided pyelonephritis are added to the differential diagnosis, which also includes torsion of an adnexal mass, degenerating leiomyoma, intrinsic gastrointestinal pathology (e.g. regional enteritis, ulcerative colitis), and uterine disease (e.g. abruption). Most laboratory tests are of little use. A diagnostic procedure often neglected in evaluating the gravida for appendicitis is to apply constant pressure over the point of tenderness and then to roll the patient to the opposite side. If the cause of pain is extrauterine the perception of tenderness persists. A moderate temperature elevation is consistent with the diagnosis of appendicitis. However, a fever which appears greater than 39ºC and is accompanied by rigors more often is associated with conditions other than appendicitis unless appendiceal rupture has occurred with resultant peritonitis. The leukocyte count and sedimentation rate may be elevated as a consequence of pregnancy. However, a differential count that is shifted to the left may be the first laboratory indication of significant appendiceal pathology. Urinalysis is helpful in excluding the possibility of right-sided pyelonephritis.

Endovaginal and graded compression ultrasonography are potentially valuable diagnostic procedures. Graded compressive ultrasonography is performed by compressing the right lower quadrant with a linear array transducer and is capable of demonstrating an inflamed non-ruptured appendix. The criteria for ultrasound diagnosis of acute appendicitis include visualization of a non-compressible aperistaltic appendix with a target-like appearance in transverse view and a diameter greater than or equal to 7 mm. The overall accuracy and specificity of ultrasonography

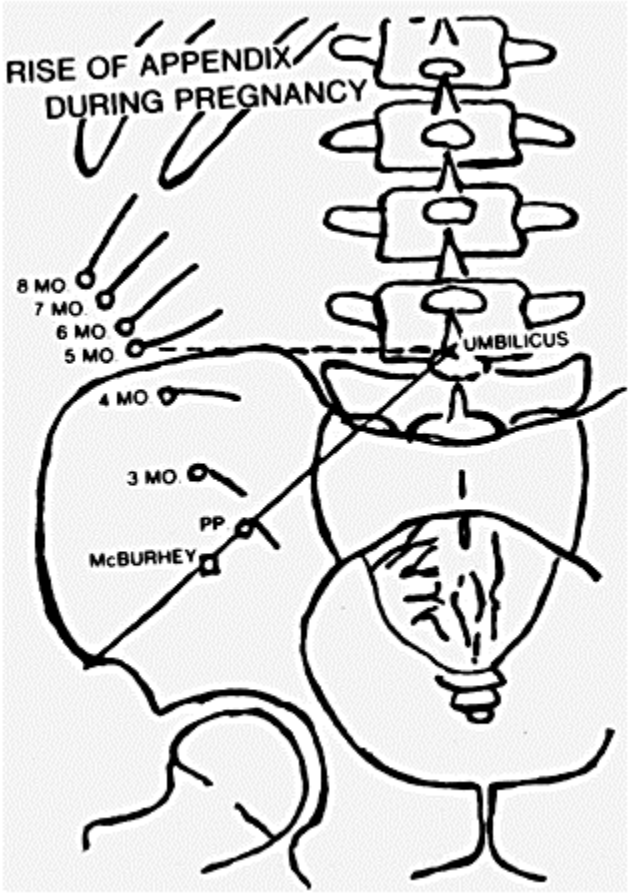

Figure 66.1 Changes in the position and direction of the appendix during pregnancy: After the fifth month of pregnancy the appendix lies at the crest level and rises above this level during the last trimester. The postpartum position of the appendix (pp)

corresponds to its position in the non-pregnant state. Roentgenologically, the base of the appendix is usually found medial to McBurney's point. The average position of the umbilicus corresponds to the point at which a line extended horizontally from the iliac crest crosses the spine (Baer JL *et al. J Am Med Assoc* 1932; 98:1359)

in making the diagnosis of acute appendicitis is over 95% in both instances. Graded compression ultrasound is approximately 98% accurate for disease in the first and second trimester. With advanced gestation, greater technical difficulties may be encountered. An alternate diagnostic tool potentially applicable to pregnant women is helical computed tomography.

The change in the position of the appendix alters the potential morbid consequences for the gravida. The displacement of the appendix out of the pelvis and into the peritoneal cavity may account for the tendency for maternal morbidity and mortality from appendicitis to be more significant as gestation progresses. Black demonstrated that, while the overall maternal mortality rate was 4.6%, it increased as gestation progressed to 10.9% in the third trimester and to 16.7% if the disease occurred intrapartum or postpartum. These data were compiled predominantly in the preantibiotic era. The more recent studies of Brant have demonstrated a collective maternal mortality rate of 2%. However, when the disease was present in the third trimester the maternal death rate was 7.3%. The mortality of appendicitis in pregnancy is the mortality of delay.' These words were written by Labler in 1908, and unfortunately still have validity today.

There is some increase in fetal wastage and perinatal mortality associated with operative intervention. In most cases aggressive early intervention and tocolysis minimize the potential adverse fetal impact. Most perinatal complications are related to the severity of disease and operative delay rather than to the operative procedure itself. The incidence of fetal loss is 1.5% or less if appendical perforation has not occurred. Preterm delivery is estimated between 5 and 14%.

The complications of appendicitis are:

(1) peritonitis;
(2) localized periappendicular abscess formation;
(3) pylephlebitis with thrombosis of the portal venous drainage;
(4) liver abscesses; and
(5) septicemia.

The acute vasculitis and inflammatory thrombosis of the blood vessels in the mesoappendix may progress to involve the portal drainage. Septic emboli from such foci of pylephlebitis may result in metastatic hepatic abscess formation and septicemia. The principal bacteria involved are the Bacteroidaceae, peptococci, and peptostreptococci.

The recommendation for therapy is to start intravenous medication with clindamycin and gentamicin; however, prospective data involving non-pregnant patients have shown antibiotic therapy is of limited benefit in cases of non-perforated appendicitis.

There is much individualization in terms of the type of incisions. The major options are a right midtransverse incision or a low midline incision. The latter not only affords adequate exposure for removal of the inflamed appendix but also permits treatment of other conditions which may simulate appendicitis.

Selected cases of appendical abscesses can be managed with ultrasonographic-guided fine needle aspiration coupled with aggressive antibiotic therapy.

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66b
Puerperal mastitis

The portals of infection influence both pathogenesis, causative organism and clinical manifestations. The portal of infection can either be a nipple fissure leading primarily to a cellulitis or ductal leading to a more occult presentation. Puerperal mastitis usually occurs in the second or third week postpartum. Puerperal mastitis involves primarily the interlobular connective tissue, causing cellulitis of the breast. Sporadic mastitis is the result of nipple fissuring.

Although staphylococci are the most frequently encountered pathogens in cases of puerperal mastitis, other bacterial species which can cause this clinical entity include beta-hemolytic streptococci of groups B, C and G and less frequently A, *Streptococcus faecalis, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae* and *Serratia marcescens*.

With mammary cellulitis, temperature is usually in excess of 38ºC and associated with rapid pulse. The febrile response may be associated with malaise, anorexia, headache and rare chills (Figure 66.2). Changes in breast milk constituency may cause the infant to refuse to suckle the infected breast. Marked systemic symptoms are rarely encountered; therefore, when one sees a patient who is breastfeeding with what appears to be an influenza-type syndrome without upper respiratory infection, one must consider the possibility of mastitis.

Ductal mastitis is associated with mammary adenitis or milk stasis. Bacteria are present in breast milk and lactiferous sinuses, secondary to skin colonization. However the presence of bacteria in lactiferous sinuses does not correlate well with the induction of mastitis.

Ductal mastitis usually occurs in the absence of nipple fissure. In many instances of ductal mastitis, pus can be expressed from the nipple of the infected breast and the symptomatology is similar to that encountered with mammary cellulitis but often less severe. The infectious process is insidious in onset and has a more protracted course than that associated with true mammary cellulitis.

Although mammary adenitis occurs in epidemic forms in hospital settings, it may be encountered two or more weeks after delivery when the mother is at home.

EPIDEMIOLOGY

Both types of mastitis are frequently due to infection by *Staphylococcus aureus*. The epidemiologic pattern of infection is such that the newborn infant becomes colonized within the nursery by a nosocomial penicillin-resistant staphylococcus. Once infection is acquired in the newborn nursery, the nose and throat of the neonate become important reservoirs of colonization from which the bacteria are passed to the mother. The milk of a high proportion of nursing mothers becomes colonized with the strain of *S. aureus* present in the oropharynx of the infant.

Approximately 50–75% of nursing personnel are known to be *S. aureus* carriers and a permanent source of penicillin-resistant organisms within the hospital environment. The infant becomes the prime disseminator of the staphylococci to the mother and to its immediate environment. Infection is almost invariably due to a hospital-acquired strain and not to one indigenous to the mother *per se,* unless maternal staphylococcal cutaneous infection antedated her hospital admission.

The determinants of disease, as opposed to colonization, are difficult to discern. At least one of these appears to be the strain virulence of the organisms. A higher rate of breast infection occurs among nursing mothers when there is a concomitant epidemic of overt *S. aureus* infection in the newborn nursery. Even then, there is not a one-to-one correlation between colonization of a neonate with a virulent strain of *S. aureus* and subsequent maternal puerperal mastitis. Given colonization of the

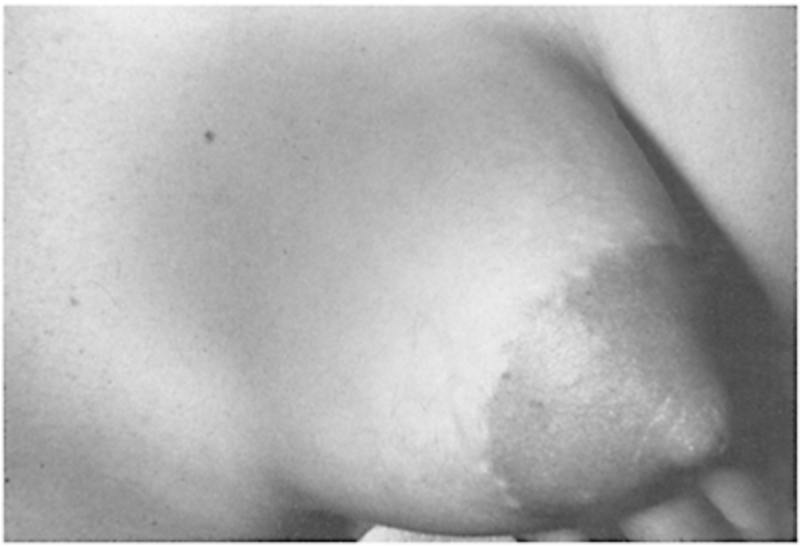

Figure 66.2 Marked erythema characteristic of acute mastitis (Marshall BR *et al. J Am Med Assoc* 1975; 233:1377)

newborn with a virulent strain some mothers will develop puerperal mastitis but the majority will not. Colonization of the newborn infant *per se* is not the sole prerequisite of the disease. Those infants colonized by non-epidemic strains of penicillin-resistant hospital-acquired staphylococci are less likely to be associated with puerperal mastitis in the nursing mother.

DIAGNOSIS

Mastitis presents with localized erythema and tenderness. A low-grade fever is usually present. Accompanying symptoms include sudden onset, generalized malaise, localized pain (usually unilateral) and rejection by the infant of the involved breast. Physical examination may reveal local edema, erythema and tenderness. The outer quadrants of the breasts are the most frequent site of involvement.

Puerperal mastitis can be distinguished from breast engorgement which has a gradual onset, is usually bilateral, presents with generalized swelling, heat and tenderness, and occurs within days of parturition. Women who have sustained a previous episode of mastitis have an increased chance of a recurrence during lactation or a subsequent pregnancy.

It is important to remember that in any type of breast infection the normal mammary architecture, more especially the ligaments of Cooper that support the parenchyma of the breast, acts as a temporary barrier to the extension of the infectious process throughout the breast. Mammary architecture may be maintained despite infection so that the fluctuance that normally accompanies abscess formation and soft tissue infection elsewhere may be masked. Infection may burrow into the breast and be much more extensive than its outward appearance may suggest.

THERAPY

For the treatment of mastitis, penicillin-resistant penicillins or selected cephalosporins have constituted the therapy of choice. Cloxacillin 250–500 mg q.i.d., dicloxacillin dosage of 125–500 mg q.i.d.,cephalexin 250–500 mg q.i.d. are the principal antibiotics prescribed in non-penicillin allergic patients. The penicillinase-resistant penicillins are highly active against both penicillinase-producing and non-penicillinase-producing strains of *S. aureus* and *S. epidermidis*. More than 90% of hospital-acquired and 70% of community-acquired staphylococci are resistant to penicillin G. In rare instances, disease may be due to a methicillin-resistant strain of *S. aureus*. If the patient is allergic to penicillin, erythromycin 250 mg q.i.d. can be used.

Despite symptomatic improvement in 24 to 48 hours, the duration of antibiotic therapy should be continued for 10–14 days.

The questions may arise as to the desirability or appropriateness of continued breastfeeding In the presence of acute mastitis. If milk stasis is a factor in the pathogenesis of the infection continued nursing to prevent breast engorgement should be encouraged.

If the infection is diagnosed early and treatment is promptly instituted, resolution is rapid and the symptoms subside over the course of one to two days. If inadequate therapy is prescribed for mastitis and infection becomes firmly established, resolution of the infectious process may not be attained and this may result in suppuration and the formation of a breast abscess. Delay in symptomatic response or increase in local tenderness warrents ultrasonographic evaluation to rule out abscess formation.

If a breast abscess is diagnosed, early surgical drainage should be instituted as soon as any evidence of a purulent collection is apparent. Cultures should be obtained from the abscess cavity and antibiotic therapy as prescribed for mastitis instituted. Persistence of infection despite antibiotic therapy without surgical drainage of a breast abscess may result in a chronic indurated breast mass or 'antibioma'. This indurated honeycomb of small abscess cavities, granulation tissue and fibrosis may lead to permanent breast deformity.

The etiological agent of the mastitis may induce disease beyond the confines of the breast.

NECROTIZING FASCIITIS/ COMPLICATIONS OF MASTITIS

The group A streptococci mastitis if not treated early may progress to what has been termed necrotizing fasciitis. Necrotizing fasciitis initially was termed by Meleney 'streptococcal gangrene'. The disease was subsequently renamed necrotizing fasciitis in order to reinforce the concept that, while progressively destroying fascia and fat, the skin and muscle are spared. Progression of cutaneous erythematous edema to pink and then blue areas of coloration in association with blisters and blebs is characteristic of this type of infection.

The clinical course is rapid, with the patient exhibiting fever (38º-39ºC) and tachycardia which occasionally is out of proportion to the fever. With the onset of the disease, the patient usually experiences pain and swelling of the affected part. Chills and tremor are not uncommon. The initial pain is replaced by numbness which, in conjunction with the toxic metabolic state, usually renders the patient indifferent to her illness. On the second to fourth day of illness, the pathognomonic signs of streptococcal gangrene occur; to quote Meleney, these are dusky hue of the skin, edema with blisters, from which can be expressed a dark serosanguinous fluid. The margins are red, and swelling is neither raised nor clearly demarcated (Figure 66.3).

On the fifth to eighth day, the discolored areas become frankly black or gray from gangrenous necrosis. Proportional to the severity of the disease, bacteremia is a common complication, with frequent metastatic involvement of the lung parenchyma. The disease process is one of extensive cellulitis complicated by abscess within fascial planes and widespread superficial fascial necrosis, resulting in separation and infarction of the overlying skin.

The basic pathologic process is a subcutaneous necrosis of the fat and fascia with a secondary occlusion and thrombosis of the dermal vessels, leading to eventual gangrene of the skin.

Diagnosis

Although a presumptive diagnosis can be inferred from the Gram stain, definitive diagnosis is contingent on bacteriologic identification. The organisms are found only in the subcutaneous slough. The surrounding edema is sterile.

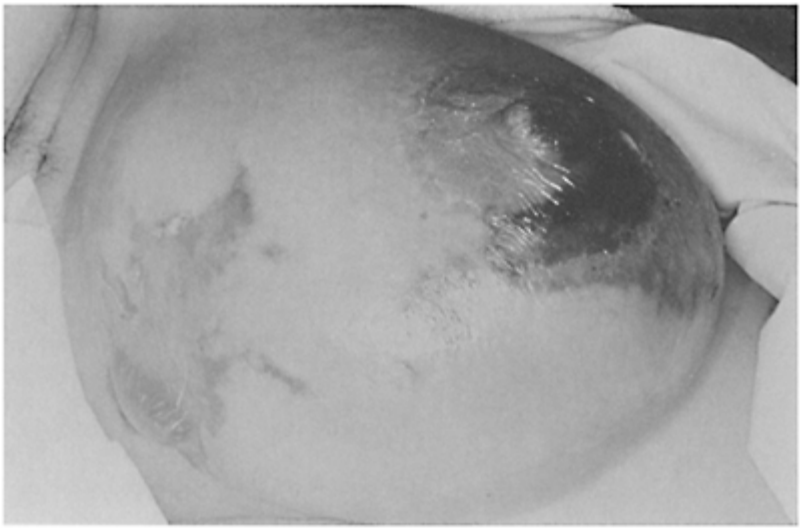

Figure 66.3 Violaceous areas with focal necrosis within an erythematous swollen breast infected with group A streptococci. Note the detachment of the superficial epidermis and presence of fluid filled bleb

Therapy

The primary therapy is aggressive antibiotic therapy and immediate operative debridement in the operating room under anesthesia. High-dose penicillin therapy (20 million units/day IV) should be started. All necrotic skin and subcutaneous tissue is removed. Delay to assess the efficacy of antibiotic therapy or local wound care is futile and leads to massive tissue loss with bowel exposure, sepsis, peritonitis, and death.

The wound must be widely opened and the necrotic material removed. Long incisions to the ends of the necrotic areas are necessary to expose the involved tissue adequately. They are generally made in a stellate fashion out from the wound. The viable overlying skin may be left intact. The whole area is irrigated and packed open. Large doses of penicillin, administered intravenously, are also necessary. Because of the nature of the destructive process and the debridement, secondary closure is not possible and healing is by secondary intention. Grafting is sometimes necessary. Once the wound is debrided, local wound care is given as indicated for the more benign infections.

MASTITIS ASSOCIATED TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) can occur in patients whose mastitis is due to TSST-1 producing strain of *Staphylococcus aureus*. Due primarily to the limited extent of disease before therapeutic intervention this is a rare event.

Toxic shock syndrome is a multisystem illness. A syndrome consisting of malaise, myalgia, low-grade fever, nausea, vomiting and/or diarrhea may antecede overt disease. In the full-blown, acute systemic illness, the patient presents with fever (>38.9ºC or 102ºF), sore throat, headache, chills, severe hypotension, myalgia, pharyngitis, conjunctivitis, leukocytosis, and generalized arthralgia. The rash is usually a consistent part of the syndrome and presents as a diffuse 'sunburn-like' blanching macular erythema. Neurological symptomatology, when present, is usually severe. Profound hypotension is one of the characteristic findings of advanced TSS. A number of abnormal laboratory findings may be observed. The white blood cell count is generally elevated but may be normal. A large left shift in the neutrophil series occurs but may not be present on the first day of illness: toxic granulation and Dohle bodies are often found and may be important diagnostic clues. Moderate elevation in liver function tests are common.

The serum amylase may be elevated. Most patients have elevations in the blood urea nitrogen (BUN) and creatinine. The platelet count often drops below 100000/mm^3 in the first week of illness. Electrocardiogram abnormalities include sinus or supraventricular tachycardia and non-specific ST segment changes, and first-degree heart block T-wave inversion is sometimes recorded in the precordial leads as are premature atrial and ventricular extrasystole. Patients with TSS may have evidence of pulmonary involvement which may be mild or progress to frank adult respiratory distress syndrome.

Diagnosis

The diagnosis is inferred by the multiorgan disease (usually with fever, headache, diarrhea, liver and renal test abnormalities) and a characteristic rash in a patient with focal disease due to *S. aureus*.

Therapy

The initial therapy is that of aggressive volume replacement and initiation of appropriate antibiotic therapy. Because of the large volume of fluids necessary, it is strongly recommended that a Swan-Ganz catheter be placed and Anesthesia be alerted that adult respiratory distress syndrome may develop in this particular patient. Concomitantly, local therapy should be directed to remove as much toxin as possible from the portal of infection. Antimicrobial therapy requires the administration of a beta-lactamase resistant semisynthetic penicillin such as oxacillin or nafcillin. A single dose of netilmicin is advocated because of its synergistic effect with the semisynthetic penicillins. Because of the probability of underlying renal damage, a second dose is rarely administered. The choice of netilmicin over gentamicin or tobramycin is based on its being the least nephrotoxic of all the aminoglycosides. The patient should be extensively monitored for the development of renal failure and/or adult respiratory distress syndrome.

66c
Breast abscess

J.Patrick O'Leary, MD

HISTORICAL BACKGROUND

The female breast has for many years been a sensuous symbol of femininity. As such, it has been revered while at the same time, neglected and disguised. Diseases of the breast have been considered disfiguring or unfeminine, and if they occurred, they were frequently ignored.

In the recent scientific literature, inflammatory disease of the breast has been overshadowed by malignant degeneration of this organ. However, this was not always true. In Breasted's translation of the Edwin Smith Papyrus, a document which was transcribed in about 3000 B.C., precise descriptions of mastitis and breast abscess were provided. Inhotep, the probable author of this manuscript, identified eight different cases of disease of the breast. Of these, only one may have been cancer, but the description is vague; and since the process occurred in a male, it may have been gynecomastia.

Hippocrates also identified acute inflammatory disease of the breast and differentiated it from malignant disease in his thesis on Diseases of Women.

Many ancient physicians treated only diseases for which a cure could be anticipated. In the Egyptian culture, if a surgeon was asked to see a patient, he could decide only one of three things. If he felt that a cure was obtainable, he made a contract to do so. If he did not feel that a cure was imminent, he must refuse to treat at all for no allowance was made for a therapeutic result short of a cure. The third alternative that he might choose was that he needed a longer period of observation before he could make one or the other of the previous decisions. The code of Hammurabi went even further, proposing physical harm be done to the physician who did not satisfy his contract for cure of the patient.

In these times, only two operations on the breast were advocated. One was amputation, while the other was the application of heat and the institution of surgical drainage.

Ancient physicians tended to avoid patients with breast cancer, while patients with breast abscess were surgically drained. Therapy of inflammatory disease of the breast had advanced little from the time of Inhotep to the advent of the recent antibiotic era.

ANATOMY

In the most simplistic terms, the breast is a modified sweat gland that is located on the anterior chest wall and which is attached to the chest musculature by suspensory bands of fascia. The glandular structure is surrounded by a layer of fat and the entire organ is encased by an envelope of skin (Figure 66.4).

Embryologically, the glandular structure migrates from the area of the axilla and in the adult a remnant of breast tissue frequently extends superiorly and laterally. This

extension is known as the axillary tail of Spence. The glandular lobes, or acini, are connected to the nipple by an arborization of lactiferous ducts. These ducts are specialized and have a surrounding structural stroma that is responsive to hormonal stimuli. An ampullary dilatation of the lactiferous ducts occurs at the apex of the breast before they open onto the surface of the nipple. These areas are known as the lactiferous ampullae, or milk sinuses. Although it appears that each duct is lined by a single layer of epithelial cells, there is a second layer of flat cells of epithelial nature that acts as a basement layer of epidermis.

The nipple is surrounded by a circular area of pigmented skin which is known as the areola. This area contains contractile smooth muscles which facilitate in nipple contraction.

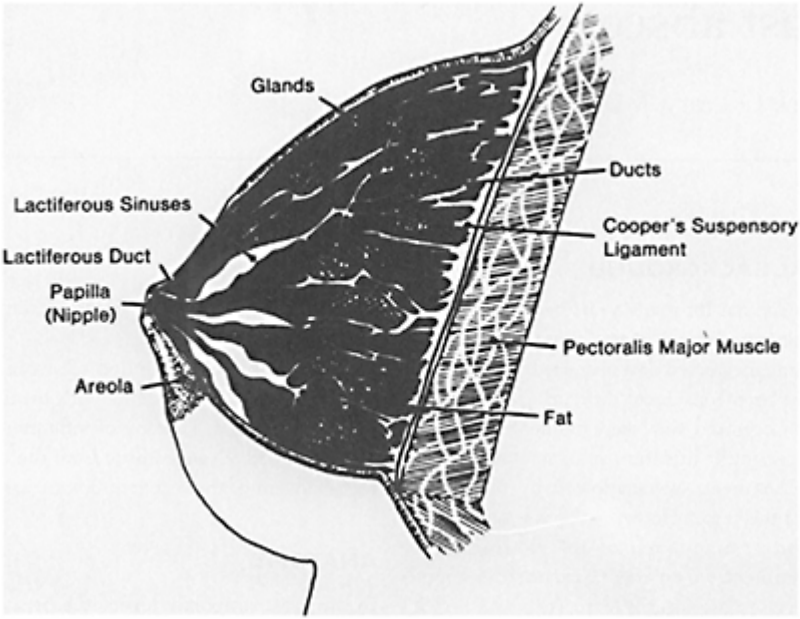

Figure 66.4 A vertical section through the breast, detailing its composite structure. Note the segmentation of the glandular aspect by the ducts and Cooper's suspensory ligaments. It should also be noted that the lactiferous duct dilates into the lactiferous sinus beneath the nipple and before the glandular structure is reached

Fiber septa run throughout the glandular aspect of the breast to support the breast. These suspensory ligaments of Cooper (Figure 66.5) attach to the deep fascia of the pectoralis major muscle and to the dermal layer of the skin. This septum provides the breast with a considerable amount of mobility and acts to segment the breast, an important consideration should inflammatory disease occur.

The skin covering the breast is transgressed by minute lines that are circumareolar in location, and then extend out from the nipple in concentric circles much as ripples in a pond. These are known as Langer's Lines (Figure 66.6) and they help to disguise scars if the incisions are appropriately placed.

CLINICAL DISEASE

Although the vast majority of breast abscesses are associated with lactation, some can occur secondary to ectasia of the lactiferous ducts. If clinical findings suggest inflammation in the non-lactating breast, the primary diagnosis to be excluded is inflammatory carcinoma. Although ectasia of the lactiferous duct would be more common, inflammatory carcinoma can mimic breast abscess and can only be diagnosed with biopsy.

Lactation mastitis has been extensively studied. In the era from the availability of penicillin to 1950, this antibiotic was found to be the drug of choice. As studies were continued and as penicillin was used more extensively, the pattern of infection changed. Initially, *Staphylococcus aureus* and beta-hemolytic streptococci were the more common pathogens. Later, staphylococci became the most common pathogen, and this was frequently noted to be of the phage-type 80/81. Prior to the advent of this particular virulent penicillinase-producing strain, the usual duration of a lesion was three to four weeks. With the more common use of

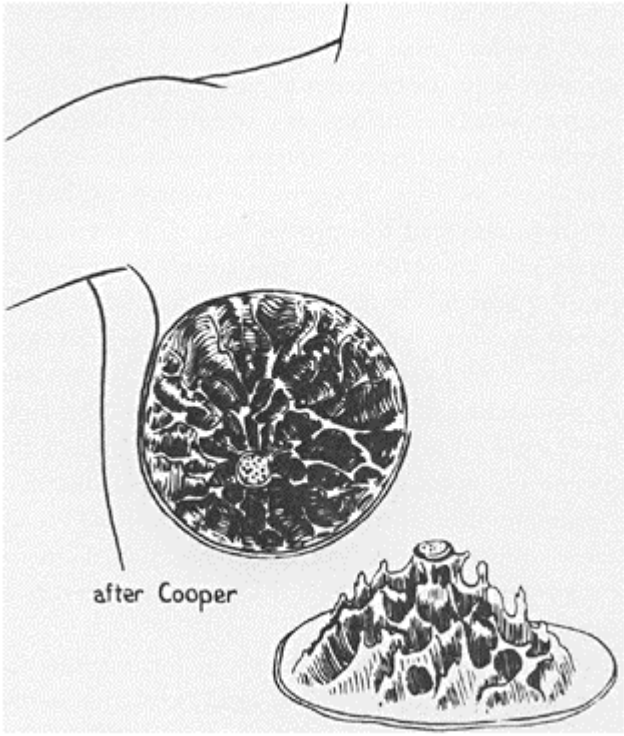

Figure 66.5 A representation of Cooper's original description of the suspensory ligaments that now bear his name. His observations were made at the time from anatomic dissection of the female breast. These suspensory ligaments provide the breast with mobility while at the same time cording the breast off into various smaller subsets

antibiotics and the change in infecting organisms, the duration of the illness has lengthened.

It has been shown that there is early colonization with *S. aureus* of babies born in maternity hospitals. The infections of the babies does not seem to be related to contamination by the mothers, as cultures of the nares or vaginas of the mothers do not correlate with cultures from the nares of the infants. This colonization of babies may come from the nursing staff. Cultures taken from the milk of nursing mothers and from the rectum and throats of their babies have shown that *S. aureus* of a similar type can be

isolated from both with great regularity. The breast milk is usually infected 24 hours after delivery, but not before delivery.

While traditionally the microbiology of breast abscess has focused on *S. aureus*, in non-puerperal breast

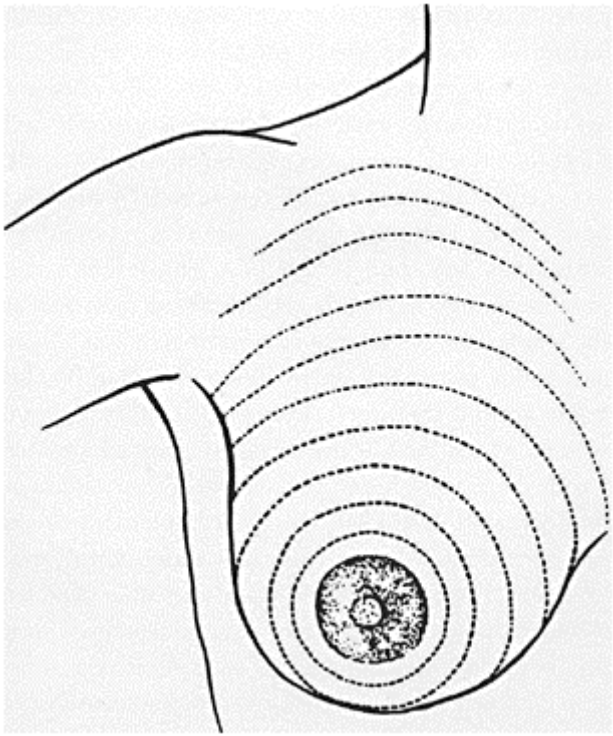

Figure 66.6 Position of Langer's lines. It should be noted that these small wrinkles in the skin form concentric circles around the nipple. Surgical incisions that are constructed to lie in these miniature crevices are cosmetically pleasing and much less deforming than radial incisions in this part of the body

abscesses, mixed anaerobic bacteria including the peptostreptococci and *Mobiluncus curtisii* are the more prevalent bacteria. There are two types of breast abscesses: one in which *S. aureus* predominates and one in which class II and III anaerobic bacteria predominate.

The skin flora of the breast plays a relatively minor role in the production of breast abscess. Bacteria gain entry to the breast more commonly through the terminal ducts or through skin fissures in the nipple. Once within the breast, the bacteria proliferate in the milk sinus and throughout the ductal tree. The ensuing inflammatory process occludes the ducts draining the stimulated glandular tissue. Since milk is an excellent culture medium, the growth of bacteria occurs rapidly.

In patients who have a periareolar abscess, pregnancy is not a common finding. The abnormality in these patients is found in the subareolar space. As the lactiferous ducts approach the surface of the nipple, they dilate to form the lactiferous sinus. This portion of the duct is lined by squamous cells and is normally quite short (less than 2 mm in length). Squamous metaplasia can occur in this area and fill the ductules with keratinous debris. Flow through the ducts is retarded and with stasis, infection is common. The inflammatory process, though having its origin immediately beneath the areola, can extend into adjacent tissue. The original description of this process by Zuska identified fistulous tracts around the areola in a small cohort of young woman. When the specimens were examined, the lactiferous ducts were found to have been obstructed with desquamated epithelial debris. Although this disease has been demonstrated to be associated with nipple inversion, Haagensen substantiated an earlier report by showing that the disease could occur in women without nipple inversion. Although there is a positive relationship between nipple inversion and periareolar abscess, the exact relationship is unknown. It is possible that in some patients the nipple inversion is a direct result of retraction of fibrous tissue from chronic inflammation, while in other patients the nipple inversion contributed to the formation of the abscess.

It is unclear whether the ectasia is primary or occurs secondary to obstruction of the ducts by the desquamated epithelium. It is clear, however, that mammary duct ectasia need not always progress to fistula, and it is probable that mammary duct fistulas can occur without ectasia.

Infection of the non-lactating breast is uncommon. If such a condition should arise, the lesion should be suspected of being inflammatory carcinoma. Similarly, the finding of a Gram-negative breast infection in a non-gravid female warrants abandonment of non-operative management in favor of tissue confirmation of the disease process.

DIAGNOSIS

The clinical presentation may vary somewhat with respect to time of onset, but most frequently occurs within the first two weeks of the nursing period. The patient generally notices that one breast becomes somewhat tender to the touch, seems to be larger, and may develop some reddening. As the process progresses, the breast becomes exquisitely tender and the patient usually complains of a sensation of heaviness. At this point, systemic symptoms of malaise, weakness, and fever can occur. If aggressive treatment is begun, the maturation of this process to a true abscess can frequently be aborted. If the breast is neglected, or if treatment is inadequate, then gradually the breast becomes less tender and an abscess develops (Figure 66.7). Frequently, the abscess will be contained in one section of the breast by the infiltrating septa of Cooper’s ligaments. Spontaneous rupture of the abscess can occur either through the nipple, but more commonly through

the dependent part of the breast. Deep sinuses can be produced that may drain for protracted periods of time if appropriate therapy is not instituted.

Ultrasound studies are valuable in documenting the presence of an abscess. Tiu *et al.* analyzed the ultrasound findings of 204 patients in whom a breast abscess had been documented. Most lesions showed grade 1 or grade 2 echogenicity (86%), smooth contours (31%), macrolobulation (31%), irregular contours (16%) and a hypoechoic rim (16%). The combination of a hypoechoic rim surrounding a fluid space or a central area of low-level echoes (grade 1–3) should strongly suggest abscess formation.

The breast abscess must be differentiated from other suppurative processes that can occur in the breast. In the acute state, the diagnosis is usually apparent. The only entity that mimics mastitis is inflammatory carcinoma, and the differentiation between these two pathologic processes is usually self-evident.

In the chronic state the differentiation between a chronic subareolar breast abscess and a lactation abscess may occur. The chronic subareolar abscess does occur in younger women, but not those who have recently undergone pregnancy and lactation. The pathophysiology of the chronic subareolar abscess begins with dilated lactiferous sinuses (milk sinuses) just below the nipple. These may become clogged with keratinous debris, and thereby produce retention cysts of the milk sinus. Disruption of this distended wall leads to

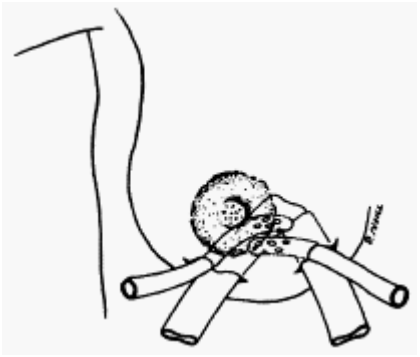

Figure 66.7 Breast abscess drainage. Adequate therapy of breast abscess includes appropriate antistaphylococcal antibiotics as well as adequate drainage. Once an abscess develops, drainage is mandatory. Dependent drainage should be obtained when possible. Although soft, flat, rubber drains are acceptable, in some larger breast abscesses larger catheters will be helpful in irrigating

the abscess cavity and providing a larger tract for drainage. When irrigation is used, the irrigating fluid can be infused through one catheter while the other catheter is used for suction. This sump system will increase patient comfort

extravasation of material into the subareolar fat and the production of an inflammatory process. Treatment of this lesion requires an appropriate diagnosis and then local resection of the involved milk sinuses.

Neglected lactation mastitis with abscess may be confused with either primary or secondary tuberculosis of the breast. The diagnosis here is made via skin testing, chest X-rays and biopsy of the chronic sinus tracts. The therapy of breast tuberculosis involves specific antituberculous drugs, as well as debridement and adequate drainage.

THERAPY

As in many other disease entities, the optimum therapy is prevention. If prevention is not possible, then early detection and aggressive therapy is the second most desirable approach. Every woman who nurses her baby is at risk to develop lactation mastitis or abscess. Since the vector to infect the breast is probably the infant, local hygiene at the level of the nipple cannot prevent the inoculation. Since this disease process frequently occurs in epidemics, when one case occurs every attempt should be made to ascertain if a *S. aureus* carrier exists in the nursery. If several cases are reported from one nursery, then all infants should have cultures of their nares prior to discharge. In addition, all employees should be cultured.

When a woman develops the signs and symptoms of lactation mastitis, she should be treated vigorously with adequate hydration, local heat to the breast, cessation of infant suckling, and appropriate antimicrobial therapy. Appropriate therapy dictates an anti-staphylococcus antibiotic administered via an appropriate route. Although oral medications may occasionally be indicated, more often the optimal route of therapy is parenteral. In many instances, intravenous administration is the most dependable and ensures the highest serum levels.

With this approach, the majority of patients with lactation mastitis will not go on to form a breast abscess.

When a lactation breast abscess occurs, nursing in the involved breast probably should be stopped. Infected serious sequelae (skin infections, staphylococcal pneumonia, staphylococcal empyema, and infant death) have been reported; however, this point of management is controversial.

Aspiration drainage

Traditional treatment of breast abscesses has involved incision and drainage under antibiotic coverage, with or without ultrasound guidance (Figure 66.7). Needle aspiration is progressively replacing surgical drainage as first therapeutic modality of choice for small abscesses.

Schwarz and Shrestha studied 30 patients with 33 breast abscesses who they treated by needle aspiration, oral antibiotics and repeated aspiration if indicated. Eighteen patients required only a single aspiration, 9 patients required multiple aspiration, and 6 required incision and drainage. By careful patient selection good results can be obtained. Imperiale *et al*. treated 26 patients with 28 acute abscesses in whom systemic antibiotic therapy had failed with serial ultrasound-guided aspiration and local injection of a broad-spectrum antibiotic. The treatment was repeated weekly until complete resolution was documented. In all but one case of a relatively large abscess did lesion volume increase at the second evaluation, this patient required surgical drainage.

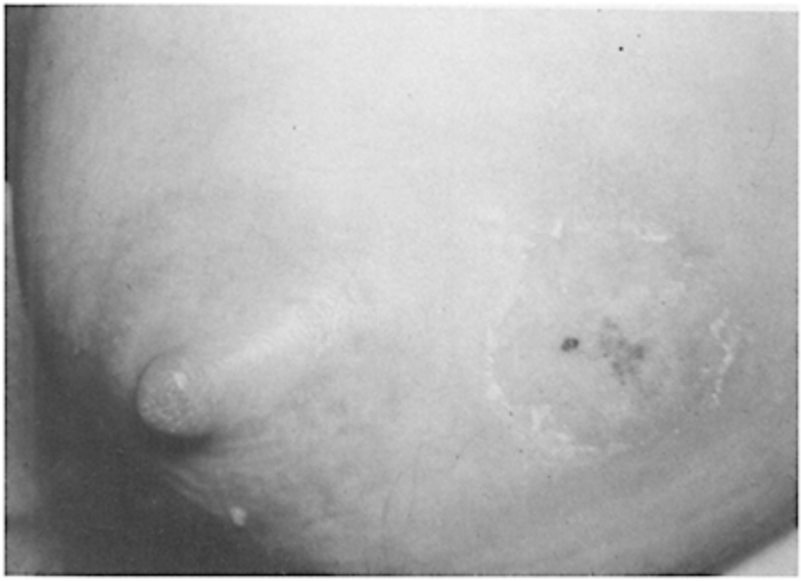

Figure 66.8 Painful erythematous indurated site of a breast abscess. (Marshall BR, *et al. J Am Med Assoc* 233:1377)

There is a need for more precise patient selection criteria to avert prolonged courses of needle aspiration or residual morbidity from delayed intervention.

Surgical drainage

If an abscess occurs, then drainage is mandatory. Because of the severe pain associated with the inflammatory process, drainage should be done under light, general anesthesia. This assures the maximum comfort to the patient and allows the surgeon to adequately decompress the abscess cavity. The incisions in the breast should be curvilinear so that they follow Langer's Lines (Figure 66.6), and in a dependent part of the breast. It is frequently necessary to make two incisions so that maximum drainage is ensured. In most instances, small, flat rubber drains are adequate. In the extensively involved breast, it may be necessary to place hollow rubber tubes so that irrigation can be accomplished. If tubes are necessary, it is frequently wise to place two tubes. These tubes can then act as an infusion catheter and sump drain, respectively (Figure 66.8). The fluid infused should be sterile saline. Antibiotic solutions add little in terms of local control and blood levels from local absorption are unpredictable, adding another unnecessary variable to the treatment regimen. If reaccumulation occurs after the initial drainage, the second area frequently can be entered so that adequate drainage can be provided without taking the patient back to the operating theater. Every attempt should be made to provide adequate drainage at the first procedure.

Dressing should be changed in the beginning every three or four hours, or when saturated. As the disease process is controlled, active granulation tissue may extrude the drains that have been placed. The flat rubber drains should be advanced beginning with the sixth post-surgical day, so that they are entirely removed on or about the tenth day. If the original incisions were discretely placed, the breast will heal with a reasonably normal configuration and without disfiguring scars.

Treatment of subareolar abscesses depends on the state of the process. In patients with an acute suppurative process, local incision and drainage with antibiotics and local treatment should be instituted. When the breast has become quiescent, then a localized core excision of the nipple including the affected lactiferous duct and surrounding granulation tissue should be accomplished. The subareolar space should be inspected closely for ectasia or metaplasia. The site of excision should be drained with a closed suction drainage apparatus that can be removed in 24 hours. At the time of excision, the patient should be given appropriate antibiotics. Although such infections have classically been caused by *S. aureus*, in recent years, Gram-negative aerobic and anaerobic bacteria have been discovered with increasing frequency. Intravenous antibiotic coverage should be directed towards such organisms.

While the standard management of puerperal abscess by incision, breaking down loculi, and dependent drainage is still the traditional mode of management, an alternative approach—curettage and primary obliteration of the cavity under antibiotic cover—can give equally good results with reduced morbidity.

With the potential for close postoperative care, an alternative approach to the conventional open drainage pack dressing method is possible. Khanna *et al.* studied the effect of incision drainage and primary closure in 50 cases of lactational breast abscess. Their failure rate was 6%. The mean healing time was 7.12 days.

Breast abscesses in the non-lactating breast are not common but may occur. Treatment is generally similar, but biopsies must be taken so that inflammatory or underlying intraductal carcinoma will be appropriately diagnosed, if present.

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67
Vaccination of women in pregnancy

IMMUNIZATION AND PREGNANCY

Antepartum, intrapartum or postpartum immunization is modified by virtue of the fact that the risk-benefit balance must be modified to address possible fetal or neonatal adverse consequences. Unfortunately considerations and recommendations as to whether or not to immunize a gravida or potential gravida are often based upon uncontrolled observations or extrapolations from non-pregnant women. Vaccine induced immunity is distinct from passive immunity which is the result of the administration of pathogen-specific antibodies.

Vaccines are categorized into two broad groups by the biological activity of the immunogen agent or agents and the type of the resultant immunity. A secondary modification is the duration of the immunity induced.

Killed vaccines

The immunogen or immunogens in a killed vaccine is usually an inactive form of the organism, a purified subcellular fragment of the organism, a genetically-engineered recombinant protein or an inactivated exotoxin. In some cases the immunogenicity of the exciting antigen has been enhanced by conjugation with a carrier protein (Table 67.1). Antigen-specific antibodies and activation of some elements of cellular immunity result from such vaccination. Detection of antigen-specific antibodies can occur usually within 7 to 10 days; however, the necessary level of immunity to abort or modify infectious challenge may take several weeks to a month to develop after vaccination. If prior vaccination has occurred, the appearance of antigen-specific antibodies is significantly accelerated. Compared to live organism vaccines, the induced immunity is of relativly short duration.

Live vaccines

The immunogen in a live vaccine is an attenuated form of the infectious agent. Despite attenuation of its pathogenicity, in a number of instances, infection-induced complications or dissemination may occur (Tables 67.2 and 67.3). The immunity derived is often life-long.

Table 67.1 Infectious pathogen vaccines potentially impacting on pregnancy

Killed vaccines	
Nonviral agents	***Viruses***
Pneumococcus (polyvalent cojugates)	Hepatitis A Hepatitis B
Typhoid (VI polysaccharide)	Influenza Poliomyelitis (inactivated)
Tetanus	
Toxoids	Rabies

Risk from vaccination during pregnancy is largely theoretical. The benefit of vaccination among pregnant women usually outweighs the potential risk when:

(1) the risk for disease exposure is high;
(2) infection would pose a special risk to the mother or fetus; and
(3) the vaccine is unlikely to cause harm.

Combined tetanus and diphtheria (Td) toxoids are the only immunobiologic agents routinely indicated for susceptible pregnant women. Previously vaccinated pregnant women who have not received a Td vaccination within the last ten years should receive a booster dose. Pregnant women who are unimmunized or only partially immunized against tetanus should complete the primary series. Depending on when a woman seeks prenatal care and the required interval between doses, one or two doses of Td can be administered before delivery. Women for whom the vaccine is indicated but who have not completed the required three-dose series during pregnancy should be

Table 67.2 Prophylaxis/immunization for viral infections in pregnancy

Virus	***Recommendation for risk from disease***	***Type of exposure***
Hepatitis A virus	**M: Increased severity in third trimester** **F:** Potential for **abortion, or premature delivery,** a function of severity of maternal illness If maternal disease is within 10–14 days of delivery, **neonatal hepatitis** may occur	**Recent exposure:** Immune serum globulin 0.06 ml/kgh IM **Serosusceptable gravida with anticipated exposure:** Inactivated vaccine 1.0 ml IM, 2 doses given 6 months apart
Hepatitis B virus	**M: Severity** of maternal disease **increases** in third trimester **F: Fetal and neonatal infection possible** Greatly increased risk of **chronic carrier state**	**Serosusceptable gravida with anticipated exposure:** Recombinant vaccine, 1.0 ml IM with repeat dose 4–6 weeks later or 1–5 months later
Influenza virus	**M: Increased severity of pneumonia** in the late second and third trimesters **F:** Very **rare congenital disease;** questionable non-specific anomalies	**Recent exposure:** None; amantadine not recommended in pregnancy **Anticipated exposure:** Killed annual vaccine before influenza season

		(November–April)
Measles virus	**M:** Potential for abortion, stillbirth, preterm delivery a function of severity of maternal disease **F:** Congenital infection can occur	**Recent Exposure:** Immune serum globulin 0.25 ml/kg within 72 hours
Mumps virus	**M:** Unchanged by pregnancy **F:** Adverse fetal outcomes a function of the severity of maternal disease **Neonatal parotitis or aseptic meningitis** may occur when maternal disease occurs in the periparturitional period	**Recent exposure:** No active intervention currently recommended
Polio viruses	**M:** If not previously vaccinated possible aspetic meningitis or poliomyelitis **F:** Fetal outcomes influenced by the severity of maternal disease	**Anticipated exposure:** Inactivated vaccine 0.5 ml, SC or IM; repeat dose at 4–8 weeks and 6–12 months later; avoid oral vaccine in pregnancy
Rabies virus	**M:** Life threatening disease **F:** Fetal outcomes influenced by the severity of maternal disease	**Known exposure:** Rabies immune globulin 20 IU/kg; if wounds are present, half infiltrated into punctures site and other half IM; otherwise all IM **and** vaccine (HDCV) 1.0 ml IM on days 0, 3, 7, 14 and 28
Rubella virus	**M:** Unchanged by pregnancy **F:** Possible **rubella syndrome, rubella embryopathy**	**Known exposure:** Immune serum globulin 0.55 ml/kg may mask maternal disease; impact on transplacental transmission questionable; not recommended for routine use
Vaccinia virus	**M:** Unchanged by pregnancy **F:** Unknown	**Anticipated exposure:** Vaccine **not** recommended in pregnancy
Varicella-zoster virus	**M:** Increased risk of pneumonia and death **F:** Possible disseminated varicella, congenital varicella syndrome	**Recent exposure:** If serosusceptible, varicella-zoster immune globulin 625 IU IM within 96 hours

Adapted with permission from MMRW 1994; 43:1

Table 67.3 Guide to contraindications and precautions to vaccination situations[1]

True contraindications and precautions	***Not contraindications (Vaccines may be administered)***
General for all vaccines (DTP, DTap, OPV, IPV, MMR, Hib, Hepatitis B)	
Contraindications	**Not contraindications**
Anaphylactic reaction to a vaccine contraindicates further doses of that vaccine or an injectable antigen[2]	Mild/moderate local reaction (soreness, redness, swelling) following a dose

Anaphylactic reaction to a vaccine constituent contraindicates the use of vaccine containing that substance[2]	Mild acute illness with or without a low-grade fever
Moderate or severe illnesses with or without a fever	Current antimicrobial therapy
	Convalescent phase of illnesses
	Prematurity (same dosage and indications as for normal full term infants)
	Recent exposure to an infectious disease[2]

DTP/DTaP (Diptheria-tetanus-acellular pertussis)

Contraindications	**Not contraindications**
Encephalopathy within 7 days of administration of previous dose of DTP	Temperature of ≤40.5ºC (105ºF) following a previous dose of DTP
Precautions	
Fever of >40.5ºC (105ºF) within 48 hours after vaccination with a prior dose of DTP	Family history of convulsions[3]
Collapse or shock-like state (hypnotic-hyporesponsive episode) within 48 hours of receiving a prior dose of DTP	Family history of sudden infant death syndrome
Seizures within 3 days of receiving prior dose of DTP	Family history of an adverse event following DTP administration
Persistent, inconsolable crying lasting ≥3 hours within 48 hours of receiving prior dose of DTP	

Notes: This information is based on the recommendations of the Advisory Committee on Immunization Practices (ACIP) and those of the Committee on Infectious Diseases (Red Book Committee) of the American Academy of Pediatrics (AAP). Sometimes these recommendations vary from those contained in the manufacturer's package inserts. For more detailed information, providers should consult the published recommendations of the ACIP, AAP, and the manufacturer's package inserts.

[1]The events or conditions listed as precautions, although not contraindications, should be carefully reviewed. The benefits and risks of administering a specific vaccine to an individual under the circumstances should be considered. If the risks are believed to outweigh the benefits, the vaccines should be withheld; if the benefits are believed to outweigh the risks (for example, while traveling in a foreign country during an outbreak), the vaccine should be administered.Whether or not to administer DTP to children with proven or suspected underlying neurological disorders should be decided on an individual basis. It is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is preferred, though IPV may be considered if a full vaccination series can be completed before the anticipated imminent exposure.

[2]Persons with a history of anaphylactic reactions following egg ingestions should be vaccinated with caution. Protocols have been developed for vaccinating such persons and should be consulted. (*J Pediatr* 1993; 102:196–9, *J Pediatr* 1988; 113:504–6)

[3]Acetaminophen given before administering DTP and thereafter every four hours for 24 hours should be considered for children with personal or family history of convulsions in siblings or parents. Adapted from *MMWR* 1994; 43:1

followed up after delivery to ensure they receive the doses necessary for protection.

There is no convincing evidence of risk from vaccinating pregnant women with other inactivated virus or bacteria vaccines or toxoids. Hepatitis B vaccine (HBV) is recommended for women at risk for hepatitis B infection, and influenza and

pneumococcal vaccines are recommended for women at risk for infection and for complications of influenza and pneumococcal disease.

Oral polio vaccine (OPV) can be administered to pregnant women who are at substantial risk of imminent exposure to natural infection. Although OPV is preferred, inactivated polio vaccine (IPV) may be considered if the complete vaccination series can be administered before the anticipated exposure. Pregnant women who must travel to areas where the risk for yellow fever is high should receive yellow fever vaccine. In these circumstances, the small theoretical risk from vaccination is far outweighed by the risk of yellow fever infection. Known pregnancy is a contraindication for rubella, measles, and mumps vaccines. Although of theoretical concern, no cases of congenital rubella syndrome or abnormalities attributable to a rubella vaccine virus infection have been observed in infants born to susceptible mothers who received rubella vaccine during pregnancy.

People who receive measles, mumps, or rubella vaccines can shed these viruses but generally do not transmit them. These vaccines can be administered safely to the children of pregnant women. Although live poliovirus is shed by persons recently vaccinated with OPV (particularly after the first dose), this vaccine can also be administered to the children of pregnant women because experience has not revealed any risk of polio vaccine virus to the fetus.

All pregnant women should be evaluated for immunity to rubella and tested for the presence of hepatitis B surface antigen (HBsAg). Women susceptible to rubella should be vaccinated immediately after delivery. A woman infected with HBV should be followed carefully to assure the infant receives hepatitis B immune globulin (HBIG) and begins the hepatitis B vaccine series shortly after birth. There is no known risk to the fetus from passive immunization of pregnant women with immune globulin preparations. Further information regarding immunization of pregnant women is available in the American College of Obstetricians and Gynecologists Technical Bulletin Number 160, October 1991. This publication is available from the American College of Obstetricians and Gynecologists, Attention: Resource Center, 409 12th Street SW, Washington, DC 20024–2188.

BREAST FEEDING AND VACCINATION

Neither killed nor live vaccines affect the safety of breastfeeding for mothers or infants. Breastfeeding does not adversely affect immunization and is not a contraindication for any vaccine. Breastfed infants should be vaccinated according to routine recommended schedules.

Inactivated or killed vaccines do not multiply within the body. Therefore, they should pose no special risk for mothers who are breastfeeding or for their infants. Although live vaccines do multiply within the mother’s body, most have not been demonstrated to be excreted in breast milk. Although rubella vaccine virus may be transmitted in breast milk, the virus usually does not infect the infant, and if it does, the infection is well tolerated. There is no contraindication for vaccinating breastfeeding mothers with yellow fever vaccine. Breastfeeding mothers can receive OPV without any interruption in the feeding schedule.

ALTERED IMMUNOCOMPETENCE

The Advisory Committee on Immunization Practices (ACIP) statement on vaccinating immunocompromised persons summarizes recommendations regarding the efficacy, safety, and use of specific vaccines and immune globulin preparations for immunocompromised persons. ACIP statements on individual vaccines or immune globulins also contain additional information regarding these issues.

Severe immunosuppression can be the result of congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy or therapy with alkylating agents, antimetabolites, radiation, or large amounts of corticosteroids. Severe complications have followed vaccination with live, attenuated virus vaccines and live bacterial vaccines among immunocompromised patients. In general, these patients should not receive live vaccines except in certain circumstances that are noted below. In addition, OPV should not be administered to any household contact of a severely immunocompromised person. If polio immunization is indicated for immunocompromised patients, their household members, or other close contacts, IPV should be administered. Measles-mumps-rubella (MMR) vaccine is not contraindicated in the close contacts of immunocompromised patients. The degree to which a person is immunocompromised should be determined by a physician.

Limited studies of MMR vaccination in HIV-infected patients have not documented serious or unusual adverse events. Because measles may cause severe illness in persons with HIV infection, MMR vaccine is recommended for all asymptomatic HIV-infected persons and should be considered for all symptomatic HIV-infected persons. HIV-infected persons on regular immunegamma globulin (IGIV) therapy may not respond to MMR or its individual component vaccines because of the continued presence of passively acquired antibody. However, because of the potential benefit, measles vaccination should be considered approximately two weeks before the next monthly dose of IGIV (if not otherwise contraindicated), although an optimal immune response is unlikely to occur. Unless serologic testing indicates that specific antibodies have been produced, vaccination should be repeated (if not otherwise contraindicated) after the recommended interval.

An additional dose of IGIV should be considered for persons on routine IGIV therapy who are exposed to measles >3 weeks after administration of a standard dose (100–00 mg/kg) of IGIV. Killed or inactivated vaccines can be administered to all immunocompromised patients, although response to such vaccines may be suboptimal. All such childhood vaccines are recommended for immunocompromised persons in usual doses and schedules; in addition, certain vaccines such as pneumococcal vaccine or Hib vaccine are recommended specifically for certain groups of immunocompromised patients, including those with functional or anatomic asplenia.

Vaccination during chemotherapy or radiation therapy should be avoided because antibody response is poor. Patients vaccinated while in immunosuppressive therapy or in the two weeks before starting therapy should be considered unimmunized and should be revaccinated at least three months after therapy is discontinued. Patients with leukemia in remission whose chemotherapy has been terminated for three months may receive live-virus vaccines.

The exact amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise healthy child are not well defined. Most experts agree that steroid therapy usually does not contraindicate administration of live-virus vaccine when the steroid therapy treatment is short term (i.e. <2 weeks); low to moderate dose; long term, alternate day treatment with short acting preparations; maintenance physiological doses (replacement therapy); or administered topically (skin or eyes, by aerosol, or by intra-articular, bursal, or tendon injection). Although of recent theoretical concern, no evidence of increased severe reactions to live vaccines has been reported among persons receiving steroid therapy by aerosol and such therapy is not in itself a reason to delay vaccination. The immunosuppressive effects of steroid treatment vary, but many clinicians consider a dose equivalent to either 2 mg/kg of body weight or a total of 20 mg per day prednisone as sufficiently immunosuppressive to raise concern about the safety of a vaccination with live-virus vaccines. Corticosteroids used in greater than physiological doses can also reduce immune response to vaccines. Physicians should wait at least three months after discontinuation before administering a live-virus vaccine to patients who have received high systemically absorbed doses of corticosteroids for 2 weeks.

VACCINATION IN THE CONTEXT OF PRIMARY CARE

Traditionally, vaccination has been primarily an issue for obstetricians and gynecologists as it impacted pregnancy. With the move towards primary care, there are at least two vaccines which require both knowledge and appropriate use by obstetricians/ gynecologists: the pneumococcal vaccine (23 valent) and the influenza vaccines.

Pneumococcal vaccine

As obstetricians/gynecologists are called upon to treat elderly patients or patients with immunodeficiency as a consequence of retrovirus infection, pneumococcal vaccination will become an important part of the proactive medical agenda. In the past, uncertainty about local reactions and the duration of protection have

Table 67.4 Recommendations for pneumococcal vaccine use

Immunocompromised adults at increased risk for pneumococcal disease include those with:	
(1)	chronic cardiovascular disease;
(2)	chronic pulmonary disease;
(3)	diabetes mellitus;
(4)	alcoholism/cirrhosis; and
(5)	adults of the age 65 or over

limited the use of pneumococcal vaccination. Currently, the use of pneumococcal vaccine should be predicated on: (1) the risk to the patient population; and (2) whether a pneumococcal vaccination has been procured six years or more previously.

The pneumococcal vaccine available before 1983 was a 14-valent pneumococcal vaccine. Since 1983, the vaccine has been a 23-valent vaccine. Patients recommended for primary or revaccination are listed in Table 67.4. Immunocompromised individuals with splenic dysfunction, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, transplantation, or hepatitis C virus have an increased risk of pneumococcal disease.

INFLUENZA VACCINE

The aborted swine flu program in 1976 was instrumental in assisting the CDC to re-evaluate its position regarding pregnancy (Table 67.5). The position of the CDC is that pregnancy itself has not been demonstrated as a risk factor for severe influenza infection, except during the largest pandemics of 1918–19 and 1957–58. However, since influenza vaccine is considered safe for pregnant women without a specific severe egg allergy pregnant women with medical conditions that increase their risk of complications from influenza should be vaccinated.

To minimize any concern over the theoretical possibility of teratogenicity, vaccine should be given after the first trimester. However, it may be undesirable to delay vaccinating a pregnant woman who has a high-risk condition and will still be in the first trimester of pregnancy when influenza activity usually begins.

Table 67.5 CDC recommendations for influenza vaccination

Annual vaccination is strongly suggested:

- For all older persons, particularly those **over 65 years,** because the risk of death during influenza outbreaks generally increases with age
- For all persons (children and adults) who are at increased risk of adverse consequences from infections of the lower respiratory tract because of a pre-existing **medical condition**

Conditions predisposing to such increased risk include:

- **Acquired or congenital heart disease** with actual or potential alterations in circulatory dynamics (e.g. mitral stenosis, congestive heart failure, or pulmonary-vascular overload)
- Any **chronic disorder** or condition that compromises **pulmonary function** (e.g. chronic obstructive pulmonary disease, bronchiectasis, heavy smoking, tuberculosis, severe asthma, cystic fibrosis, neuromuscular and orthopedic disorders with impaired ventilation, bronchopulmonary dysplasia following neonatal respiratory distress syndrome)
- **Chronic renal disease** with azotemia or nephrotic syndrome
- **Diabetes mellitus** or other metabolic diseases
- **Severe chronic anemia,** such as sickle cell disease

- Conditions that **compromise the immune mechanism,** including certain malignancies and immunosuppressive therapy

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68
Urinary tract infections in pregnancy

PATHOPHYSIOLOGY

The gestational hormones of pregnancy have been demonstrated to have a profound effect on smooth muscle. Loss of tonicity occurs within the uterine musculature in preparation for its enlargement and the accommodation of an expanding intracavitary mass. Comparable changes occur in all smooth muscle organs early in gestation. A significant variation can be demonstrated from individual to individual. The magnitude of the phenomenon is thought to be mediated through the density of hormone receptor sites.

The effect of the gestational hormones on the musculature of the urogenital tract significantly increases the residual volume of urine in the ureters following micturition. The non-gravid female will have a residual urine volume of 5–15 ml. With gestation, this volume increases to approximately 20–60 ml (Figure 68.1). Not all individuals exhibit this phenomenon. In some instances the changes may be limited to a single ureter. Other individuals will maintain a normal ureteral configuration, as determined by intravenous pyelography, throughout the pregnancy.

Because of a second point of fixation involving the right iliac artery, there is a tendency for the right ureter to accommodate for the physiologic elongation by kinking. This phenomenon is thought to be responsible for the predominance of symptoms on the right side when pyelonephritis develops as a consequence of ascending infection.

EPIDEMIOLOGY

The classic work of Edward Kass focused attention on asymptomatic bacteriuria as a critical point of intervention. In the absence of unique factors which predispose to asymptomatic bacteriuria (ABU) (i.e. sickle cell trait), the incidence of asymptomatic bacteriuria is inversely proportional to the socioeconomic level of a given population. Indigent patient populations have a rate between 6 and 8%, approximately twice that observed in private patients. Asymptomatic bacteriuria develops early in the course of pregnancy; 75% of women who will develop asymptomatic bacteriuria during pregnancy have greater than 100000 colonies of bacteria per milliliter of urine at the first prenatal visit. Statistically, 25–30% of gravidas with asymptomatic bacteriuria will progress to pyelonephritis. If asymptomatic bacteriuria is aggressively treated, the incidence of pyelonephritis drops precipitously. Asymptomatic bacteriuria reflects either recent infection by a constituent of the vaginal flora or chronic renal parenchymal disease with seeding from above. The ideal point of therapeutic intervention is that of infection (asymptomatic bacteriuria), not that of disease (cystitis, pyelonephritis).

Schieve *et al.* examined the effects of antepartum urinary tract infection on adverse maternal and perinatal outcomes. Crude and multivariable analyses were performed with a perinatal registry cohort of 25 746 mother/infant pairs. Elevated risks were observed for exposure to urinary tract infection and low birth-weight, prematurity, preterm low birthweight, premature labor, hypertension/pre-eclampsia, maternal anemia, and amnionitis. Urinary tract infection was associated with perinatal death only among subjects 20 to 29 years of age.

Prior to the 1970s, infections of the urinary bladder or renal parenchyma were designated by the term -itis, which was applied to the site of organism replication; hence the terms urethritis, cystitis, and pyelonephritis. The perception of the inability to preclude renal parenchymal involvement in patients with asymptomatic bacteriuria and cystitis, coupled with the need to

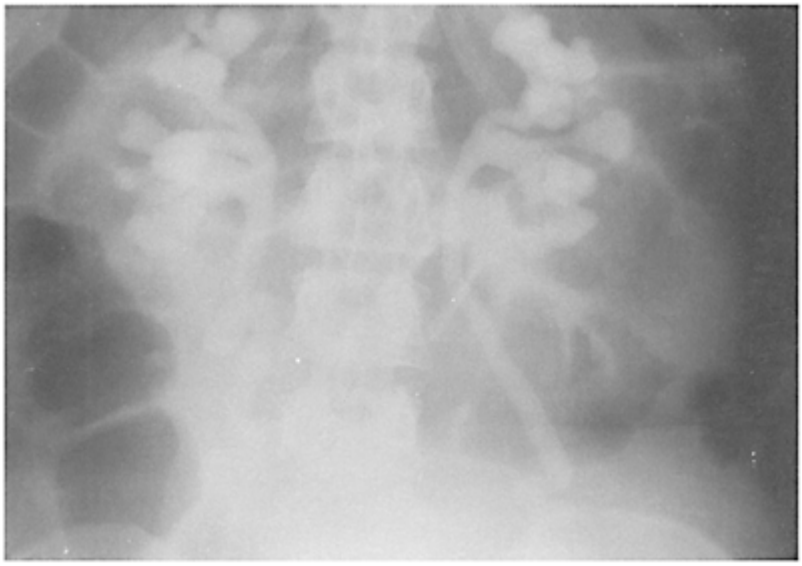


Figure 68.1 Intravenous pyelogram demonstrating a pseudohydronephrosis as a consequence of smooth-muscle relaxation which is responsible for marked increase in residual volume of urine during pregnancy

individualize therapy, resulted in the adoption of a broad-label term of urinary tract infection (UTI) to designate a spectrum of involvement which differs significantly in its biologic significance.

Critical in the diagnosis of urinary tract disease is its distinction from infection. Gram-positive and Gram-negative aerobic bacteria can replicate in significant quantity in urine without eliciting laboratory or clinical evidence of disease. Asymptomatic bacteriuria at a

given point of time becomes the cornerstone of therapeutic management. By its diagnosis and therapy, one can frequently abort the progression from infection to disease, and in so doing, implement the pinnacle of therapeutics—preventive medicine.

ASYMPTOMATIC BACTERIURIA

All diagnostic tests except appropriately obtained urine cultures lack either sensitivity or specificity. Bachman *et al.* compared the existing rapid screening techniques for detection of asymptomatic urinary tract infections. The screening tests of urinalysis, urine dipstick, and Gram's staining were compared to the results of standard urine culture at an initial prenatal visit. In followup visits, urine dipstick testing was compared with urinalysis. Rapid screening tests for asymptomatic infection in pregnant women revealed the following: Gram's staining identified 22 of 24 patients (sensitivity, 91.7%; specificity, 89.2%); urine dipstick, 12 of 24 (sensitivity, 50%; specificity, 96.9%); and urinalysis with presence of leukocytes, six of 24 (sensitivity, 25%; specificity, 99%). In follow-up visits, urine dipstick tests detected 19 infections and urinalysis, three (positive predictive value, 5% compared with 3%). Urine dipstick testing for nitrites identified half of all patients with UTIs and was superior to urinalysis on follow-up visits. Although Gram's staining is more expensive, it was more accurate than urinalysis or urine dipstick test for nitrites. Urinalysis was never the test of choice because it detected fewer positive cultures. Leukocyte measurement correlated poorly with asymptomatic urinary tract infection.

Since there are no clinical signs or symptoms, asymptomatic bacteriuria (ABU) is diagnosed by prospective culture monitoring of urine. The major problem in diagnosis of ABU is not quantification or bacteriologic identification, but rather proper collection of urine specimens for analysis. With very rare exceptions, urinary tract infection is monoetiological in character. When more than one kind of bacteria exist in a clean mid-stream voided specimen, it is probable that prior to collection, the urine came in contact with one or both labia minora and majora. To be authenticated, the diagnosis of mixed infection requires that the same isolates be obtained from a specimen obtained by catheterization or suprapubic aspiration.

For the specimen to have diagnostic validity, the perineum should be cleansed with an antiseptic solution such as povidone-iodine and the patient instructed in the technique required to obtain a valid specimen.

The diagnosis of ABU is predicated upon demonstrating more than or equal to 100000 colonies of a single bacterial genus on two consecutive specimens. A colony count of 50000 colonies per ml of urine obtained from a catheterized specimen should be viewed with suspicion, and additional tests should be undertaken to exclude ABU. ABU may be due either to the *de novo* acquisition of bacterial replication via ascending urethral infection or seeding of the urine from above due to chronic smoldering pyelonephritis. The distinction is of great therapeutic importance. In the case of the former, eradication of the bacteria can be readily achieved with bolus or short-term administration of an appropriate antibiotic. Chronic smoldering disease requires long-term therapy.

The major diagnostic problem is how to distinguish between these two entities. Localization as to the site of ABU can be achieved by ureteral catheterization, bladder

washout techniques, and the analysis of IgG antibody-coated bacteria. The former are invasive techniques which are of purely academic interest. Only the antibody-coated bacteria determination is a noninvasive technique. It is predicated upon the fact that with parenchymal involvement and the elicitation of an inflammatory response, the body responds by elaborating specific antibodies which ultimately adhere to the bacterial surface. Specific bacterial fluorescence can be demonstrated by using an anti-IgG, fluorescence-tagged antibody. Unfortunately, the occurrence of false-positive and false-negative results have limited this test's usefulness.

CYSTITIS

Cystitis is differentiated from asymptomatic bacteriuria by the concomitant presence of clinical symptomatology as well as bacteriuria and pyuria. As with asymptomatic bacteriuria, cystitis, in the absence of mucosal denudation, is rarely a cause of fever. The probability of added maternal urinary tract morbidity is low with uncomplicated cystitis; however, once bacteriuria is documented in a pregnancy, serial monitoring of the urine is advocated to exclude the urinary tract from being a reservoir for bacteria which may cause perinatal septicemia in the periparturitional period.

Dysuria

Dysuria occurs because of the loss of urethral or bladder mucosal integrity. The difference in pH between intraand extracellular fluid (7.47) and urine (4.5–8.0) causes a biophysical reaction which registers as a burning sensation. The timing when dysuria occurs is of diagnostic importance. Dysuria at the beginning of micturition indicates involvement of the outer urethra and is most often caused by a vulvovaginitis or occult infection with *Neisseria gonorrhoeae*. Dysuria associated with urinary bladder infection occurs characteristically at the end of urination. By itself, dysuria correlates with a positive urine culture in approximately 65% of cases.

Frequency

Frequency as a symptom referable to infection is defined as the passage of small amounts of urine. In the simplest sense, the urinary bladder is nothing more than a smooth-muscle sac with peristaltic activity. The submucosal edema and the resultant loss of distensibility induced by the inflammatory response renders the urinary bladder less tolerant to volumetric expansion. Frequently, if a significant inflammatory neuritis is present, the patient complains of a suprapubic tenderness or lower midline back pain.

Pyuria

Pyuria in combination with bacteriuria is 99% specific for urinary tract infection. The diagnosis of pyuria is established by demonstrating greater than 8 white blood cells (WBC) per mm^3 upon the viewing of at least 10 high power fields.

Pyuria alone does not correlate well with urinary tract infection owing to problems inherent in specimen collection or distal urethral inflammation due to trauma or a sexually transmitted disease.

Urine dipstick or automated microscopy have been advocated as cost effective screening modalities for the detection of urinary tract infections.

Demonstration of a positive test for urine leukocyte esterase and/or nitrate is valuable. The problem with this test is its sensitivity and inability to detect bacteriuria in the absence of inflammation. Its minimum threshold is approximately 5 WBC per high power field. This value may vary based on the test strip's manufacturer. A positive leukocyte esterase test warrants evaluation. A number of other conditions not associated with urinary tract infection may cause pyuria.

Bacteria possessing nitrate reductase can also be detected using the dipstick test. The test appears to have a low sensitivity for bacteria between 10^3 and 10^5 cfu. A number of urinary tract pathogens, such as *Staphylococcus epidermidis, S. aureus, Enterococcus* species and *Pseudomonas* species lack nitrate reductase. Van Nostrand *et al.* found that 78.8% of samples containing a nitrate reductase did not produce a positive reaction with the dipstick. A positive test is a mandate for culture confirmation and therapy in pregnancy.

PYELONEPHRITIS

Whereas asymptomatic bacteriuria and cystitis are very rarely the cause of fever, pyelonephritis is. The diagnosis of pyelonephritis is implied by the recovery of greater than 100000 colonies of a single bacterial species from a patient with exquisite costo vertebral angle (CVA) tenderness and by the demonstration of clumped WBC and WBC casts in the urinary sediment. The latter are best demonstrated in spun sediment of a fresh urine sample whose specific gravity is greater than 1.020.

CVA tenderness is due to the rapid volumetric expansion of the renal parenchyma due to the inflammatory response and the resultant stretching of the renal capsule. If the capsule of the kidney is stripped away, disease of the renal parenchyma is occult unless it involves major vessels which carry their own innervation. Unless CVA tenderness is present or a large area of denuded bladder mucosa is present, it would be difficult to ascribe fever to UTI.

In the majority of instances, pyelonephritis is the potential end-titration point for ABU. Parenchymal disease of the kidney (pyelonephritis) is rarely occult. Characteristically, the patients are febrile. Physical examination reveals definite CVA tenderness.

The majority of females who will develop pyelonephritis in pregnancy are readily discernable. Seventy percent of gravidas who have pyelonephritis during gestation will have had an antecedent history of prior urinary tract infection. Smoldering chronic pyelonephritis tends to have an associate pedigree of repeated episodes of urinary tract infection in early childhood, honeymoon cystitis, and pyelonephritis in a preceding pregnancy, etc.

Pyelonephritis identifies two patient populations: those in whom bacterial infection of the renal parenchyma antedates the acute episodes, and those in whom the smooth muscle

alterations induced by pregnancy unmask an occult dysfunction of the ureterovesicular junctions. In the case of the former, renal involvement may reflect reactivation of pre-existing disease; in the case of the latter, infection is acquired *de novo* and parenchymal involvement is the consequence of ascending infection.

In the absence of obstruction, pyelonephritis is a self-limited disease owing to segmental compartmentalization of the kidney. The demonstration of a true obstruction due to calculi constitutes a medical emergency. Unless the obstruction is relieved, total parenchymal involvement ensues.

LIMITATIONS ON ANTIBIOTIC USE

Pregnancy limits the antibiotic spectrum that can be utilized in the treatment of UTI. The use of fluoroquinolone or the tetracycline class of antibiotics is contraindicated in pregnancy because of either potential for teratogenicity or induction of an embryopathy.

When parturition is imminent, restrictions should be placed on trimethoprim/sulfamethoxazole. Sulfonamides readily traverse the placental barrier and achieve cord drug levels comparable to those in the maternal circulation. The sulfonamides should not be used in the treatment of high-risk pregnancies once fetal viability has been established. Following parturition, the sulfonamides will competitively displace bilirubin from its albumin carrier, and it is the free bilirubin that traverses the blood-brain barrier and induces kernicterus in the neonate. The presence of sulfonamides precludes using total bilirubin levels as a prognostic index of ensuing kernicterus. If an infant is born with significant sulfonamide levels in the cord blood, an exchange transfusion is advocated. The fluoroquinolones produced permanent lesions in the cartilage of immature dogs.

MANAGEMENT OF URINARY TRACT INFECTION IN PREGNANCY

Asymptomatic bacteriuria

At the time of registration and six weeks prior to the expected date of confinement, all new prenatal patients should be cultured for ABU. Unless the patient has one of the following:

(1) prior history of pyelonephritis, or
(2) diabetes mellitus or sickle-cell-related diseas.

A second specimen should be obtained at 32–36 weeks. For patients in the indicated high-risk categories, more frequent monitoring is needed. The documentation of ABU is an indication for therapy (Table 68.1).

Of all ABU isolates, 90% belong to the *Enterobacteriaceae*. The therapy of asymptomatic bacteriuria is either a bolus administration with amoxicillin or augmentin or a standard course of an appropriate antibiotic. In the past, the selection of an intermediate semi-synthetic penicillin or sulfonamide as first-line therapy had been not

predicated upon a drug-of-choice concept, but rather upon cost-efficacy considerations. Ampicillin will eradicate only 60% of the causative organisms and should be used for empiric therapy only when follow-up cultures are obtained in 24–36 hours. The cost difference between ampicillin and an oral cephalosporin may be of such magnitude as to preclude drug purchase by the patients, particularly those from a lower socioeconomic background.

Irrespective of which antibiotic is administered, a test of cure should be obtained 24–36 hours after the onset of therapy. If a given antibiotic is effective against the urinary tract pathogen, the urine will be sterile in less than 24 hours. If bacteriuria is still demonstrable after 24–36 hours of therapy, the bacterial isolate should be identified and its antibiotic susceptibility pattern established by the Kirby Bauer method. Table 68.2 summarizes the drugs of choice for the individual urinary tract pathogens.

Current therapy favors the use of single dose therapy. There is no convincing evidence that a long course of medication is more effective than a short one. Villar *et al.* reviewed the data involving over 400 women as to the duration of treatment for ABU. All studies compared single dose treatment with four to seven day treatments. No differences in 'no-cure' rates was detected. Longer duration of therapy was associated with an increase in reports of adverse drug effects.

Cystitis

For premenopausal, non-pregnant women, single-dose antimicrobial therapy is generally less effective than the same antibiotic used for a longer duration. Most antimicrobial agents given for three days are as effective as those given for longer duration and adverse events tend to be found more often with longer therapy. Trimethroprim or cotrimoxazole can be recommended for therapy only in communities when resistance to uropathogens is 10% or less. The fluoroquinolones are the standard drugs of

Table 68.1 Therapeutic recommendations for urinary tract infections in pregnancy

Indication	***Modifier***	***Recommended therapy***	***Follow-up***
Asymptomatic bacteriuria: due to GBS, *E. coli, Proteus mirabilis, S. saprophyticus*	No prior history of pyelonephritis. If prior history, evaluate for L-form variant (presuming one is dealing with a Gram-negative isolate)	Least expensive betalactam antibiotic	Test of cure
Due to resistant *E. coli, Klebsiella pneumoniae, Enterobacter* species, etc.	(See above)	Resistant—*E. coli* oral cephalosporin or IM aminoglycoside, *K. pneumoniae* oral cephalosporin	Test of cure

Either of the above	PRIOR HISTORY OF PYELONEPHRITIS at any time prior to or during pregnancy	(See above)	Culture monitored throughout pregnancy
	Prior episode of ABU or cystitis in this pregnancy	Prophylactic antibiotics either daily or postcoitus	Test of cure
Cystitis	No prior history of pyelonephritis	Antibiotic selection initially predicated on regional isolation data; ultimate selection by isolate antibiotic sensitivities. AVOID using nitrofurantoins	Test of cure
Pyelonephritis		Third generation (bid) cephalosporin. Ultimate selection based on isolate antibiotic sensitivity profile (see separate protocol)	Culture monitored throughout pregnancy. If recurrent UTI, consider nitrofurantoin prophylaxis
			PRIOR HISTORY OF PYELONEPHRITIS, rule out L-form variant when isolates identical in each case

GBS, group B Streptococci; ABU, asymptomatic bacteriuria

choice unless *Escherichia coli* resistance exceeds 10%. Alternate therapy includes fosfomycin, tromtamol or beta-lactams, such as the second- or third-generation cephalosporins or pivmecillinam.

Single dose therapy is also not recommended for acute cystitis because early pyelonephritis can be mistaken for uncomplicated cystitis.

In pregnancy the use of a fluoroquinolone is contraindicated for fetal indications.

Pyelonephritis

Pyelonephritis occurs in 1–2% of all obstetric patients. It is the most common medical complication during pregnancy requiring hospitalization. The protocol for dealing with pyelonephritis in pregnancy is bedrest, aggressive hydration and systemic antibiotics (Table 68.3). The patient should be switched to oral medication after 24 hours and a repeat quantitative

Table 68.2 Drugs of choice for urinary tract pathogens in pregnancy

Bacteria	***Drug of choice***
Gram-positive	Ampicillin
Staphylococcus epidermidis	
Micrococcus subgroup III	
Group B beta-hemolytic streptococci	
Group D streptococci (enterococci)	
Gram-negative *(Enterobacteriaceae)*	Determined by sensitivities
Escherichia coli	65% susceptible to ampicillin
	80% susceptible to cefazolin
	90% susceptible to cefamandole
Klebsiella pneumoniae	Cephalosporin
Enterobacter spp. (cloacae)	Carbenicillin
Proteus mirabilis (indole-negative)	Ampicillin
Proteus vulgaris, etc. (indole-positive)	An aminoglycoside or cephalosporin (if susceptible *in vitro*)

urine culture performed. If the repeat urine culture again demonstrates greater than 100000 colonies per ml of urine of the same bacteria, antibiotic therapy should be changed if it can be documented that the patient received the medication initially prescribed.

The critical issues in the therapy of pyelonephritis have been well worked out. Basically:

(1) pyelonephritis is a monomicrobial disease process; in less than 1% of cases co-infection between *E. coli* and *Klebsiella pneumoniae* may be present;
(2) the urinary tract is an aerobic environment and its pathogenic spectrum is readily identifiable with comparatively simple microbiological methodology;
(3) material for valid microbiological identification of the pathogen is easily attainable;
(4) in the absence of obstruction and/or advanced diabetic vascular disease, the anatomical compartmentalization limits the resultant morbid consequences; and
(5) most of the drugs effective in this disease process have significant renal elimination resulting in drug concentrations which are augmented in comparison to most other organ systems.

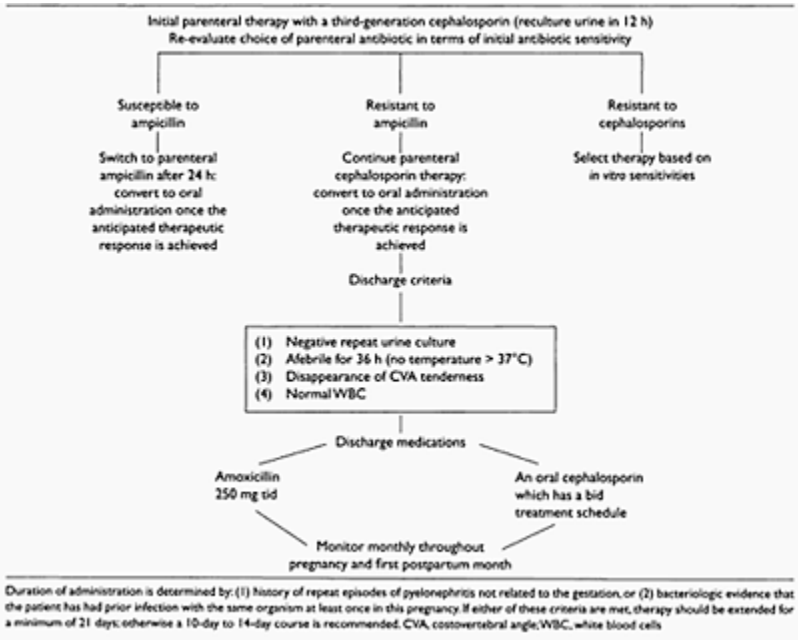
Traditionally, when a patient presents with pyelonephritis in pregnancy, urine and blood cultures would be taken and a presumptive commitment to therapy would be implemented. Approximately 90% of all cases of pyelonephritis are due to Gram-

negative rods. Ten to twelve percent of the cases involve Gram-positive organisms, i.e. group B streptococci, *Staphylococcus saprophyticus*, etc.

The selection of the initial antibiotic is often governed not by efficacy but by lower acquisitional cost; i.e. ampicillin vs. cephalosporin. One in every three to four cases of pyelonephritis treated with ampicillin will be a therapeutic failure. This is in contrast to an observed failure rate of one in seven to eight patients for a first- or second-generation cephalosporin. Frequency of administration significantly impacts on the total cost to the patient. When computed, the cost of isolated clinical failures often erases the economies achieved with successful therapeutic interventions in the majority of patients.

Once the diagnosis of pyelonephritis in pregnancy is confirmed, the patient should be placed on broad spectrum second- or third-generation cephalosporin with more greater than bid frequency of administration.

Table 68.3 Sequence for the evaluation and management of pyelonephritis during pregnancy



Duration of administration is determined by: (1) history of repeat episodes of pyelonephritis not related to the gestation, or (2) bacteriologic evidence that the patient has had prior infection with the same organism at least once in this pregnancy. If either of these criteria are met, therapy should be extended for a minimum of 21 days; otherwise a 10-day to 14-day course is recommended. CVA, costovertebral angle; WBC, white blood cells

The current cephalosporin of choice is ceftriaxone (1–2 g IV once daily). Blood cultures are of limited value unless:

(1) Gram stain of urine reveals Gram-positive cocci, suggestive of *Staphylococcus aureus;*
(2) the patient has experienced rigor; or
(3) the patient's clinical condition is unstable.

Approximately 20% of patients with pyelonephritis develop occult renal dysfunction similar to acute tubular necrosis. The decrease in renal function is transient, but in isolated instances may persist for three to five weeks after termination of therapy. Baseline evaluation of renal function, including electrolytes, blood urea nitrogen and creatinine, is deemed advisable.

Another 1–4% of women with acute pyelonephritis will manifest septic shock or adult respiratory distress syndrome (ARDS) due to sustained high multiplicity bacteremia due to Gram-negative bacteria. Administration of antibiotics can function as a catalytic event which converts the warm-phase of shock into its clinically more significant variant. An increase in respiratory rate in a gravida with pyelonephritis should warrant obtaining blood gases and a chest roentgenogram. Unlike most etiologies of ARDS, the prognosis is good with appropriate therapy.

Confirmation of antibiotic efficacy can be done within hours after the initiation of antimicrobial therapy. Demonstration of continued significant bacteriuria by Gram staining of the urinary sediment or culturing using bacterial culture kits four hours after the initiation of parenteral antibiotic therapy and aggressive hydration should be interpreted as indicative of a therapeutic failure. Under these circumstances, the antimicrobial regimen should be changed to a third-generation cephalosporin and an aminoglycoside with a broader coverage for the *Enterobacteriaceae*.

Once the lysis of fever and marked amelioration of CVA tenderness has occurred, conversion from parenteral to oral antibiotics should be implemented. As a rule of thumb, the cost to the patient of intravenously administered antibiotics is 10 to 15 times that of per oral administration. Which antibiotic is chosen is governed by *in vitro* sensitivity studies and cost of acquisition. If the urinary pathogen is sensitive to ampicillin, conversion from parenteral therapy to an oral cephalosporin cannot be advocated other than for reasons of patient compliance.

Failure of CVA tenderness to respond to therapy as predicted by *in vitro* antibiotic testing may be due to either:

(1) inaccurate laboratory data;
(2) obstructive uropathy; or
(3) an independently functioning disease process.

In a gravida with suspected urosepsis on the basis of obstructive uropathy, ultrasonography is the procedure of choice.

Ambulatory treatment of acute pyelonephritis

Medical economics have renewed the debate as to whether acute pyelonephritis in pregnancy should be deemed a mandate for hospitalization.

Clinical studies have shown that low-risk gravidas in the first and early second trimesters can, after an initial period of observation and *in vitro* microbiological confirmation of effective therapy, be effectively treated on an ambulatory basis.

Millar and Cox treated 120 pregnant women with acute pyelonephritis at 24 weeks gestational age or less with either an intramuscular or intravenous cephalosporin. If clinically stable at the end of 24 hours, the patients chosen for ambulatory care therapy were discharged home. The patients then completed a 10-day course of oral cephalexin 500 mg qid. Ten percent of outpatients were rehospitalized because of sepsis, abnormal laboratory tests or 'recurrent pyelonephritis'.

Wing conducted a similar therapeutic study, focusing on gravidas after 24 weeks' gestation. After eliminating 154/256 potential study candidates for reasons which included sepsis, respiratory compromise, recurrent pyelonephritis, urological abnormalities, allergies to cephalosporins/penicillins etc, they were left with 92 eligible participants. Thirty percent of the outpatient subjects had to remain in the hospital because of clinical sepsis, documented bacteremia or a non-responsive WBC count. Another 13% failed therapy.

Outpatient therapy for acute pyelonephritis in early pregnancy will require a valid signed informed consent.

FOLLOW-UP OF PATIENTS WITH URINARY TRACT INFECTION

Once a UTI is documented in pregnancy, the patient should be screened on a monthly basis, including the first postpartum month.

Whether to place a patient on chronic antimicrobial suppressive therapy versus close monitoring is an issue open to debate. Plan and Sacks evaluated the effectiveness of prophylaxis for recurrent UTI during pregnancy. During 39 pregnancies, 33 women with a history of recurrent UTIs (and, in some instances, pyelonephritis) received postcoital prophylaxis consisting of a single oral dose of either cephalexin (250 mg) or nitrofurantoin macrocrystals (50 mg). While 130 UTIs occurred during a mean observation period of 7 months before prophylaxis, only a single UTI occurred during pregnancy after prophylaxis. Problems with compliance with medication stresses the need for bacteriological surveillance in the chronically suppressed group.

Table 68.4 Significance of positive cultures following initial therapy for pyelonephritis

Bacterial Species	***Follow-up urine specimen***	
	24–48 hours after hospitalization	***7–10 days after therapy or at any other time during gestation***
Same organism	1. Inappropriate antibiotics	Relapse: Most often indicative of chronic smoldering pyelonephritis+ L-phase variant transformation. Rule out possibility of structural abnormalities of the urinary tract
	2. Failure to receive medication	
	3. Acquired resistance (R factor)	

Different organism	Mixed infection unmasked by therapeutic elimination of dominant organism	Reinfection:Attempt to rule out mechanized factors or problems with personal hygiene which may predispose to reinfection. Underlying chronic pyelonephritis not uncommon

Following the initial episode of ABU, culture monitoring of the gravida is advocated. If the urine is sterile after therapy, the preferred choice is to monitor the patient. If ABU or overt disease recurs, culture and sensitivity tests are indispensible in determining the biologic significance of this event and whether one is dealing with either relapse or reinfection.

The reappearance of greater than 100000 colonies per ml after the bacteriological evidence of cure (as documented by sterile urine cultures within a week of therapy termination) mandates the differentiation of relapse from reinfection. If the bacteria isolated during the second episode exhibit a different pattern of antibiotic susceptibility from that originally isolated or are of a different genus, the infection is termed a reinfection. If the bacteria is the same in terms of genus and antibiotic sensitivities, the infection is termed a relapse. The distinction is important in terms of pathogenesis and prognosis. Reinfections often represent a problem in terms of hygiene of the female genital tract. Pyelonephritis, when it occurs in this setting, is of limited morbid consequence and no urological workup is indicated in the postpartum period. If educational steps cannot effectively alter the chain of events producing disease, these patients are good candidates for chronic prophylactic suppression. The most effective drug for long term, low-dose prophylaxis is nitrofurantoin 50–100 mg, given at night. More recent studies show that a dose administered on alternate nights, 3 nights a week or after intercourse is just as effective.

Postcoitus antibiotic prophylaxis with nitrofurantoin should be considered for women in whom episodes of urinary tract infection are associated with sexual intercourse.

Relapse may be indicative of a chronic smoldering form of renal parenchymal disease. Once relapse has occurred, the patient should be closely monitored for renewal of parenchymal bacterial replication. If the patient has a prior history of urinary infection at some time other than pregnancy, it is our policy to advocate monthly monitoring for a two-year period and to obtain an intravenous pyelogram approximately six to 12 weeks postpartum (Table 68.4).

SIGNIFICANCE OF URINARY TRACT INFECTION FOR MOTHER AND FETUS

Monitoring for asymptomatic bacteriuria should probably be considered one of the essential components of prenatal care.

Traditionally, the potential adverse effects of asymptomatic bacteriuria have been conceptually limited to the development of pyelonephritis. Recent evidence suggests that those species of *Enterobacteriaceae* which are able to establish numerically significant representation in the genitourinary tract by virtue of their augmented ability to adhere to cell surfaces differ from other species of *Enterobacteriaceae* which may be transient constituents of the perineal and vaginal flora. Gravidas with asymptomatic bacteriuria, as

opposed to gravidas who have one or more members of the *Enterobacteriaceae* in the perineal or vaginal flora but who do not have asymptomatic bacteriuria, are at augmented risk for postpartum endometritis and Gram-negative septicemia, and their offspring are at augmented risk for perinatal septicemia due to the *Enterobacteriaceae*.

The ability to colonize the urinary tract successfully (asymptomatic bacteriuria) in women is frequently associated with the concomitant appearance of the organism as a constituent of the bacterial flora of the posterior vaginal pool and endocervix. Monif *et al.*, in a retrospective analysis of *Enterobacteriaceae* septicemia in the immediate postpartum period, revealed that when concomitant blood, urine; and endometrial cultures were available, almost invariably the same genus isolated from the blood could be recovered from the urine and endometrium. In only one case was there any evidence of renal parenchymal involvement. Minor antibiotic sensitivity differences between the bacterial isolates from blood, urine, and endometrium suggested that not the urinary tract, but rather the maternal implantation site afforded the portal of infection. When gravidas were prospectively monitored, the incidence of postpartum endometritis following spontaneous vaginal delivery was 10- to 20-fold greater for those with asymptomatic bacteriuria than for those without.

Preliminary evidence suggests that at least 50% of cases of perinatal septicemia (defined as the onset of disease within the first 24 hours of life) occur in infants born to gravidas who have chorioamnionitis and/or ABU. That bacteria may have access to the fetus *in utero* has been suggested by the demonstration that lymphocytes of selected neonates born to mothers whose gestation had been complicated by significant urinary tract infection would undergo blast transformation when exposed to the specific strain of bacteria responsible for maternal infection.

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69
Bacterial endocarditis in pregnancy

EPIDEMIOLOGY

Infectious endocarditis superimposed upon pregnancy is a rare condition (Figure 69.1). The estimated incidence is 0.005–0.015% of pregnancies. The associated maternal mortality is a partial function of therapy. In the pre-antibiotic area, the maternal and fetal mortalities approached 75–100%. With antibiotic therapy, maternal mortality has decreased to an approximate 30%, and even this figure is misleading because of the increasing reliance on valve replacement when confronted with indications for cardiac surgery. Maternal mortality for women whose pregnancies are complicated by infectious endocarditis is four times that of women cured of endocarditis prior to pregnancy

Infectious endocarditis in pregnancy involves three high-risk groups:

(1) acute disease in gravidas undergoing abortion and subsequent sepsis;
(2) gravidas with high velocity flow cardiac lesions, i.e. bicuspid aortic valves, ventricular septal defect, or lesions such as idiopathic hyper-tropic subaortic stenosis and probably mitral valve prolapse. Atrial septal defects are low pressure cardiac lesions and hence are not at augmented risk for infectious endocarditis; and
(3) gravidas who are parenteral drug abusers.

What you do in pregnancy and when you do it are governed primarily by maternal considerations; however, given a reasonably hemodynamically stable gravida, fetal considerations can modify when you do it. A management schema which augments maternal jeopardy to enhance fetal outcome necessitates valid patient participation and consultation. Once the criteria for valve replacement have been met, and if age is consistent with a reasonable probability of a good fetal outcome, the tendency has been to deliver the fetus prematurely in order to avoid intraoperative risks to the fetus. Burstein *et al.* have reported successful cardiopulmonary bypass with subsequent aortic valve replacement immediately after an emergency Cesarean section in a case of acute gonococcal endocarditis complicated by fetal distress at 30 weeks gestation as a result of maternal cardiovascular decompensation. When surgery and/or the postoperative course requires effective anticoagulation, the risk of internal bleeding to the fetus as well as to the mother is introduced.

Since 1957 the following bacteria have been found to produce endocarditis in pregnancy:

(1) **Gram-positive cocci:**

Staphylococcus aureus,
viridans streptococci,
group B streptococci,
Peptostreptococcus anaerobius;

(2) **Gram-positive rods:**

Listeria monocytogenes;

(3) **Gram-negative cocci:**

Neisseria gonorrhoeae;

(4) **Gram-negative rods:**

Salmonella enteritidis,
Haemophilus aphrophilus.

A single case of polymicrobial endocarditis disease occurred in a heroin addict and was caused by *S. aureus* and a group B streptococcus.

While maternal mortality has dramatically dropped due to more aggressive use of open heart surgery, fetal mortality continues to be high. Zitnik *et al.* reported on 21 patients who underwent cardiac surgery with

Figure 69.1 Infectious endocarditis involving the mitral valve of a 23-year-old gravida with mitral valve prolapse

cardiopulmonary bypass. While their maternal mortality was 5%, fetal mortality was 53%.

Sexton *et al.* reported two fatal cases of acute endocarditis involving the aortic valve which occurred in a woman after a normal pregnancy and delivery and in the second woman after a second trimester abortion. Both women were thought to have normal heart valves before the onset of their infection. Of the 19 cases of pregnancy-associated group B streptococcal endocarditis, the majority of cases occurred in the pre-antibiotic stage. The principal site of involvement was the mitral valve, the site of disease being governed

by pre-existing valvular disease. When aortic valve involvement occurred, the majority of women had pre-existing congenital cardiovascular anomalies or rheumatic valvular disease. Both of these women with acute aortic valvulitis due to the group B streptococci went on to develop annular abscesses and died.

Prior to the advent of penicillin, *N. gonorrhoeae* was responsible for 6–12% of cases of infectious endocarditis. With the introduction of effective antimicrobial therapy, acute gonococcal endocarditis has become an exceedingly rare event. As is characteristic of most acute cases of endocarditis in pregnancy, the aortic valve is preferentially involved. Acute valvular perforation and the resultant aortic regurgitation are to be anticipated. The majority of women with postpartum gonococcal endocarditis require valvular replacement.

Infectious endocarditis can be classified into three broad groups based upon diverging pathogenesis:

(1) naked valve endocarditis (congenital and acquired);
(2) prosthetic valve endocarditis; and
(3) addict endocarditis.

The mortality of the three subsets is different:

(1) naked valve endocarditis 15–40%;
(2) prosthetic valve endocarditis 20–60%; and
(3) addict endocarditis 0–30%.

The subset influences the site of vegetations. In naked valve endocarditis, the vegetations tend to occur on the edge of the valves, whereas in prosthetic valve endocarditis they

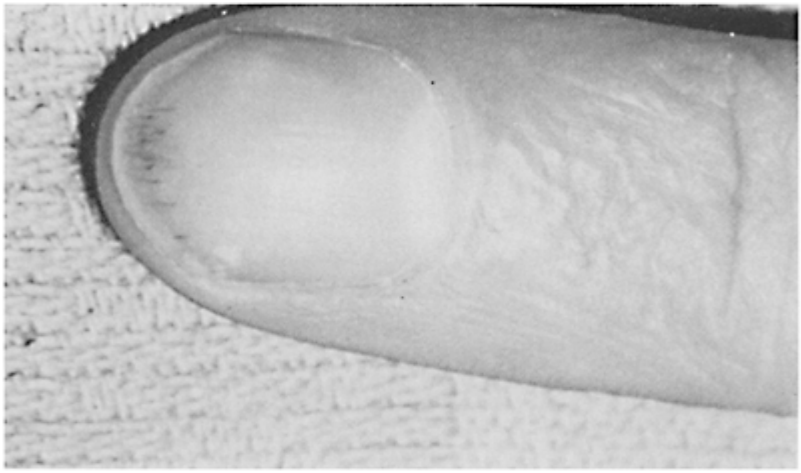

Figure 69.2 Splinter hemorrhages under the nail-bed of a male addict with infectious endocarditis

occur at the base of the annular rings. In addict endocarditis there is increased right-sided valvular involvement. The bacteriology is markedly influenced by the categories. With naked valve endocarditis, greater than 50% of cases are due to streptococci. With addict endocarditis, more than 50% of the cases are due to staphylococci.

DIAGNOSIS

The clinical presentations of infectious endocarditis are primarily those of:

(1) prolonged fever of unknown origins (FUO);
(2) FUO+arterial emboli to brain, kidneys, spleen or extremities; and
(3) congestive heart failure with regurgitative murmur and FUO.

A presumptive diagnosis of infectious endocarditis must be entertained when a FUO is documented in high-risk groups such as:

(1) congenital heart disease except low flow shunts;
(2) rheumatic valvular disease;
(3) prosthetic heart valves; and/or
(4) drug abusers.

Clinical manifestations suggestive of infectious endocarditis and particularly due to *S. aureus* are:

(1) hemorrhagic infarcts in extremities;
(2) presence of pericarditis (indicates extension of abscess through annularring); and
(3) infectious endocarditis in an addict.

On physical examination, one looks for: Osler's nodes (painful red nodules on tips of fingers and toes); Janeway's lesions (painless hemorrhagic nodules on palms and soles); Roth's spots (hemorrhagic spots with central white area on fundoscopic examination), and splinter hemorrhages under the nail-beds (Figure 69.2).

A definitive diagnosis requires recovery of a potential pathogen from the intravascular compartment and/or demonstration on two-dimensional echocardiography of vegetation. In addicts suspected of having right-sided infectious endocarditis, serial chest roentgenograms may reveal transient pulmonary infiltrates.

In suspected cases of infectious endocarditis, at least three sets of blood cultures should be taken at three different intervals (at least 30–60 minutes apart). Additional sets of blood cultures obtained to exclude possible skin contamination are not cost-effective.

If skin decontamination is done with concern and the syringe needle is changed prior to inoculation of the aerobic and anaerobic blood culture bottles, the probability of contamination is negligible. Multiple sets of blood obtained in a single time frame require clinical clarification if the physician wants all the sets to be processed. NEVER divide a single sample into multiple sets of blood cultures. It is better to put 10 ml of blood into each culture bottle than to submit 2 sets of blood cultures with 5 ml in each bottle.

The criteria for diagnosis of infectious endocarditis include:

(1) regurgitative murmur or documentation by cardiac catheterization of valvular insufficiency PLUS positive blood culture;
(2) FUO and appropriate murmur;
(3) FUO and echocardiographic demonstration of vegetations; and
(4) persistently positive blood cultures.

The differential diagnosis involves:

(1) atrial myoma;
(2) collagen-vascular disease, especially systemic lupus erythematosus (SLE);
(3) acute rheumatic fever with mitral regurgitation;
(4) chronic meningococcemia; and
(5) fever of unknown etiology.

THERAPY

When endocarditis is complicated by pregnancy, parenteral antibiotics given for four to six weeks are indicated. The continued commitment to therapy is predicated on progressive clinical and cardiovascular improvement. The choice of antibiotic is dictated by the bacteria involved. With GBS endocarditis, therapy involves a beta-lactam antibiotic plus an aminoglycoside. Vancomycin is used in patients with penicillin hypersensitivity. Persistence of fever, cardiovascular decompensation, development of new conduction defects or evidence of valvular perforation may precipitate emergency valve replacement. Infectious endocarditis should NOT be treated in community hospitals. Treatment should be carried out in an institution where bypass surgery can be performed. The response to antibiotic therapy needs to be monitored with daily blood cultures through defervesence (temperature continuously less than 37.6ºC). For intravenous therapy, scalp-vein needles should be used when possible. When and if conversion to oral therapy is needed, the *in vitro* minimal inhibitory concentration of the drug must be achieved *in vivo* as documented by measured blood concentrations.

The duration of therapy is four to six weeks for naked valve endocarditis and six to eight weeks for prosthetic valve endocarditis.

Bad prognostic signs in infectious endocarditis are the development of new conduction defects, indicating possible septal abscess which may progress to third degree heart block and/or congestive heart failure present. The sudden development of congestive heart failure with concomitant cardiomegaly argues strongly for valvular replacement.

The indications for surgical intervention are:

(1) congestive heart failure or hemo-dynamically significant mitral regurgitation;
(2) suppurative pericarditis;
(3) appearance of second or third degree atrialventricular block;
(4) persistence of febrile course after more than one week of effective antibiotic therapy;
(5) difficult to eradicate agent, i.e. pseudomonas infectious endocarditis,
(6) large vessel embolism with an organism other than viridans streptococci; and
(7) presence of large vegetation as documented by echocardiographs associated with significant hemodynamic dysfunction.

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Part IV
Problem Areas: Gynecology

70
Infectious vulvovaginitis

Herman L.Gardner, MD. Revised by Michael S.Burnhill, MD, DMSc

One-third of all the women of childbearing age currently have one or more vulvovaginal infections. Despite the discovery of highly effective, specific therapeutic agents against most vulvovaginitis, the overall incidence has not been favorably affected.

Obstetrics and Gynecology residents and medical students are not receiving adequate training in the diagnosis and management of vulvovaginal infections. Perhaps too often we strive to make every gynecology resident a superspecialist in radical pelvic surgery, hormonal chemistry, or laboratory genetics, but at the same time, grossly neglect some of the more useful aspects of his/her training. How sad it is when our star chief resident passes the American Board examinations without a falter and displays a superior knowledge of dozens of rarities in the specialty, but, after his flawless performance, falters when attempting to instruct others in how to prepare a saline wet mount of vaginal secretions. Those in training deserve more instruction in the disorders that affect hundreds of times more women than those afflicted with rare neoplastic diseases or endocrinologic problems, some of which will never be observed in a lifetime of practice.

Candida albicans, Trichomonas vaginalis or *Gardnerella vaginalis* are found in approximately 90% of all patients with vulvovaginitis. For this reason, these organisms are selected for specific analysis.

RELATIVE PREVALENCE OF THE VARIOUS VULVOVAGINITIDES

Table 70.1 shows the relative prevalence of the various infections in 1000 consecutive private patients with vulvovaginitis. Patient material included only those

Table 70.1 Prevalence of various vulvovaginitides in 1000 consecutive patients with lower genital infections—gonorrhea and syphilis excluded

Disease entity	*Incidence*	
	Number	*Percentage*
Gardnerella vaginalis vaginitis	425	42.5
Candidiasis	373	37.3

Trichomoniasis	142	14.2
Herpes genitalis	94	9.4
Condyloma acuminatum	72	7.2
Candida glabrata vaginitis	13	1.3
Molluscum contagiosum	7	0.7
Non-venereal bacterial vaginitis	7	0.7
Tinea cruris	3	0.3
Behcet's syndrome	3	0.3
Pediculosis pubis	2	0.2
Herpes zoster	1	0.1
Crohn's disease	1	0.1

patients being seen for the first time or old patients having vaginitis for the first time. New infections developing subsequently in either group are not included. Many of the women had mixed infections. Atrophic and pediatric vaginitis, gonorrhea, and syphilis are not included in these statistics.

Of the 1000 consecutive patients with vulvovaginitis, one had five infections, two had four infections, four had three infections, and 126 had two infections. Of the 425 patients yielding *G. vaginalis*, 99 (23.3%) yielded one or more other pathogens. Of the 372 patients with candidiasis, 66 (17.7%) yielded one or more other pathogens. Of the 142 patients yielding trichomonads, 53 (37.7%) yielded one or more other pathogens. Of 91 patients with herpes genitalis, 15 (16.4%) yielded one or more other pathogens. This was a surprisingly low figure. Of 72 patients with condylomata, 40 (55.6%) yielded one or more other pathogens.

LABORATORY PROCEDURES

Physiologic saline wet mount

Microscopic examination of the physiologic saline wet mount is the most important laboratory method for the differential diagnosis of vaginitis or discharge, and it should be employed in the investigation of every case. Probably, it should be used as a procedure for screening every gynecologic patient, whether she has signs and symptoms or not (Table 70.2).

Preparation of a saline mount requires only a few simple steps: a small cotton-tipped applicator is dipped into fresh physiologic saline and a drop of the solution is transferred to a glass slide. Using the same cotton-tipped applicator, a small amount of vaginal secretion is mixed with the saline on the slide. This suspension is coverslipped and examined microscopically through both low- and high-power objectives. Only when a delay in examining the slide is anticipated is a transport media tube—Transcult®—useful

in preserving the vaginal discharge in a sterile media advisable. Vaginal discharge can be examined or recultured after a delay of several hours. Old saline can become contaminated with various microbes and cause confusion.

Lactobacilli are easily visualized in the saline wet mount and the three most common organisms that cause vaginitis can usually be identified readily by finding motile trichomonads (Figure 70.1), the clue cells of *G. vaginalis* (Figure 70.2), or the spores and filaments of *Candida* (Figure 70.3). *G. vaginalis,* being a surface organism, does not provoke an out-pouring of leukocytes and for this reason never accounts for a truly pruritic discharge. A large number of leukocytes in vaginal secretions of patients with *G. vaginalis* vaginitis indicates an associated cause such as trichomoniasis. Additionally, the presence of large numbers of leukocytes may indicate contact dermatitis or infection with another bacterial process. Parabasal epithelial cells in younger women suggest the impact of *Lactobacillus* overgrowth syndrome and may also be seen when associated with large numbers of leukocytes in the presence of an active trichomoniasis. Of course, a high percentage of parabasal cells might suggest an atrophic vaginal wall from estrogen deprivation.

Potassium hydroxide (KOH) wet mount

Use of KOH, 10%, can detect up to two-thirds of candida present if the infection is principally in the hyphal phase. The use of Gram's stain raises the detection rate by allowing rapid identification of the spore forms as well. Use of KOH (10–20%) wet mount is a highly accurate method for diagnosing candidiasis. It is prepared by using a tiny drop of solution on the slide. An excess of solution can make a smear too dilute and can pose a danger to the microscope objectives. An applicator stick is used to transfer a small amount of the vaginal secretion to the slide and mix the secretion with the KOH solution. The slide is then cover-slipped and examined microscopically through both the lowand high-power objectives. Most of the cellular material on the slide dissolves immediately or becomes transparent, making detection of intact candida particles easy. While KOH clears vaginal material rapidly, keratinized cells from the vulva usually require heating the slide over a gentle flame to give a quick clearance.

Candida species are the only vaginal fungi with both spores (conidia) and filaments (hyphae). Spores in large numbers without associated filaments suggest *Candida glabrata* infection. Scrapings from the vulva which show both spores and filaments offer essential proof of the presence of *Candida,* while filamentous forms alone usually mean tinea cruris, most often a *Trichophyton* species.

INTERPRETATION OF THE SIGNS AND SYMPTOMS OF VULVOVAGINITIS

While an astute clinician can often make a correct diagnosis on the basis of clinical features alone, laboratory confirmation is always desirable, not only for the physician's feeling of comfort, but also for a possible medicolegal back-up.

Table 70.2 Clinical laboratory features of normal vaginal secretions and the most frequent causes of discharge

Features	***Normal***	***Trichomoniasis***	***G.Vaginalis vaginitis***	***Candidiasis***	***Atrophic vaginitis***	***Cervical leukorrhea***	***Lactobacillus overgrowth***
Symptoms							
Discharge	0	+−+++	0−++	0−++	0+	+−+++	0−++
Pruritus	0	0−+++	0−0+	+−+++	+−++	0	0
Burning	0−+	0−+	0	+	+	0	+
Dysuria	0	0−+	0	0−++	++	0	0
Dyspareunia	0	0−+	0	0−++	++	0	++
Characteristics of discharge							
Amount	0−+	+−+++	0−++	0−++	+	+−++	0−++
Consistency	Curdy	Homogeneous	Homogeneous	Curdy or thrush patches	Serous or mucopurulent	Mucoid or mucopurulent	Thick White
Color	White or slate	Gray or greenish	Gray	White or slate	Variable	Clear	Opaque
Odor	0	+−+++	+−++	0	+	0	0
Frothiness	0	+(10%)	+(7%)	0	0	0	0
PH	3.8–4.2	5.5–5.8	5.0–5.5	4.0–5.0	6.0–7.0	6.0–7.0	3.8–4.0
Gross tissue changes							
Vagina							
Erythema	0	0−+++	0	0−++	+	None	0
Swollen papillae	0	+(10%)	0	0−+	0−+	0	0
Petechiae	0	+(10%)	0	0	+(10%)	0	0
Ulcerations	0	0	0	0	0−+	0	0
Vulva							
Erythema	0	0−++	0	+−+++	0−+	0	0
Edema	0	0−++	0	0−+++	0−+	0	0
Excoriations or ulcers	0	0−+	0	0−+	0−+	0	0

Laboratory findings							
Wet mount							
Clue cells	0	0	+	0	0	0	0
Trichomonads	0	+	0	0	0	0	0
Spores and filamants	0	0	0	+	0	0	0
Leukocytes	0–+	++++	0–+	+–+++	+++	0–++	0
Parabasal cells	0	+–+++	0	0	+++	0	0
Bacteria	Large rods	Mixed	Small rods	Large rods	Mixed	Lactobacilli	Increased Lactobacilli
Stained smears	Lactobacilli, diphtheroids	Mixed bacteria bacilli	Short Gram-neg. diphtheroids	Lactobacilli	Mixed	Lactobacilli	Lactobacilli Stripped nuclei
Cultures	Lactobacilli or diphtheroids predominate	*Trichomonas vaginalis*	*Gardnerella vaginalis*	*Candida* species	Mixed bacteria	Lactobacilli	Lactobacilli

The most meaningful examination of a patient with a vaginal infection or discharge is one made when the patient is experiencing symptoms, when she has not douched for at least two or three days, and when she has not used a vaginal medication or a contraceptive jelly or cream for at least several days to a week or more. The vaginal flora is changed by chemicals circulating in the vaginal pool. Almost any chemical agent instilled into

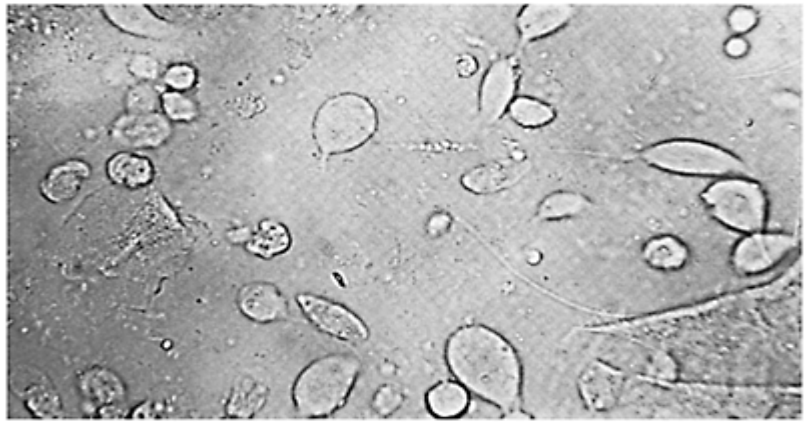

Figure 70.1 Mixed small and larger trichomonads seen under high power magnification

the vagina shortly before examination distorts the clinical pattern and makes isolation of an infectious agent difficult, if not impossible. Some medications have a residual effect, lasting several days.

Pruritus

Pruritus is a symptom, a sensation creating the urge to scratch. A patient's complaint of Vaginal itching' almost always means vulvar itching. The vagina probably never itches, apparently because it lacks the nerve endings that convey the sensation.

Vulvar itching, in the presence of a visible discharge is usually the result of trichomoniasis or candidiasis. However, as mentioned at the end of this chapter, chemical irritants are frequently the cause of the pruritus. Vulvar itching especially in young women is usually the result of trichomoniasis or candidiasis. Some years ago, trichomoniasis was considered the most frequent cause of pruritus, but since the introduction of antibiotics, oral contraceptives and metronizadole, candidiasis is easily the leading cause. With the use of metronidazole, the occurrence of trichomoniasis has been markedly reduced; and with the widespread use of antibiotics, candidiasis incidence has increased. Pruritus in women of childbearing age suggests candidiasis first and trichomoniasis second, whereas pruritus in postmenopausal women brings to mind atrophic vaginitis, vulvar dystrophy, or diabetic vulvitis. Most pruritus is accounted for by one of the causes mentioned, but innumerable other conditions such as *Candida glabrata* vaginitis, pinworms, papilloma virus, and contact dermatitis may account for other etiologic sources for pruritus.

Discharge

The term discharge, when used by the patient, is considered a symptom, and by the physician to describe a sign. While discharge has long been used synonymously with leukorrhea, meaning white discharge, few are, in fact, white. Simple accounting shows that vaginitis is the number one cause of discharge and not cervicitis, as so often taught. When vulvovaginal secretions are abnormal in volume, color, consistency or odor, the term discharge is applicable.

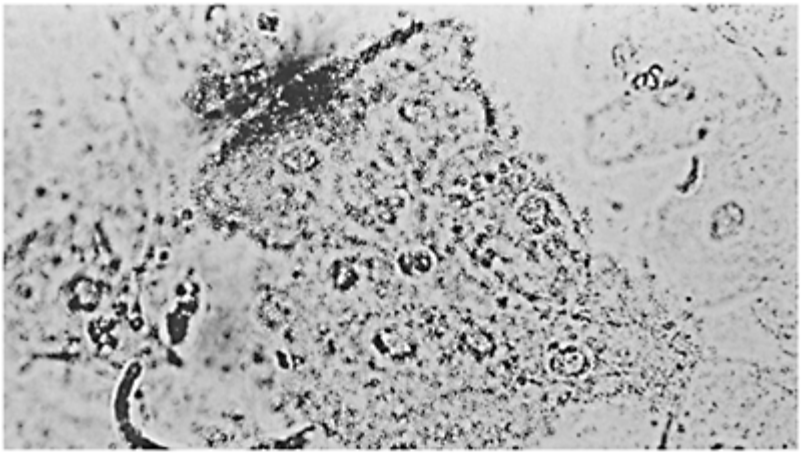

Figure 70.2 Clue cell—Note 'moth-eaten' irregular cell margins

Normal secretions

To classify a vaginal secretion as a discharge, it is first necessary to know the physical characteristics of normal secretions. Women without vaginitis or cervicitis who have good estrogen levels from either endogenous or exogenous sources have white or transparent secretions (mainly clumps of epithelial cells in serous vaginal transudate) with a consistency described as epithelial-like or curdy. The term is not interpreted to mean thrush patches or curds seen in some patients with candidiasis. A so-called curdy secretion has body and does not flow as does a homogeneous secretion sometimes described as runny, milky, or creamy

When tested with hydrion paper (Micro-essential Laboratory, Inc., Brooklyn, NY) or other pH indicator paper, normal secretions on the unlubricated, withdrawn vaginal speculum are one of the fastest, yet one of the most informative tests available. A vaginal pH of 3.8–4.2 essentially eliminates the possibility of certain infections, such as *G. vaginalis* vaginitis; of those whose pH is over 5.0, practically all will have *G. vaginalis* vaginitis if no trichomonads are present in the vaginal secretions.

Normal vaginal secretions are usually not malodorous. A few women with grossly normal secretions with a normal pH and a lactobacillus flora will still complain of an objectionable odor. Many such patients exercise poor hygiene of the vulva, with the odor developing from bacterial action on urine and smegma. Also, women with hirsutism and increased apocrine gland activity are particularly prone to develop malodor from saprophytic bacterial action on the secretions.

In general, it can be said that any patient without subjective symptoms who has a normal volume of white or clear, curdy vaginal secretion with a pH of 3.8–4.2 and no unusual odor has a normal vaginal secretion and not a discharge. The acidific rods, lactobacilli or diphtheroids, usually dominate the flora of the normal vagina.

Table 70.2 summarizes the usual clinical and laboratory findings for the most frequently found types of vulvovaginitis. As can be seen in this table, a profuse, malodorous discharge associated with pruritus always suggests trichomoniasis; a scant to moderate malodorous discharge without irritative symptoms suggests *G. vaginalis* vaginitis; and severe pruritus without significant discharge or odor suggests candidiasis.

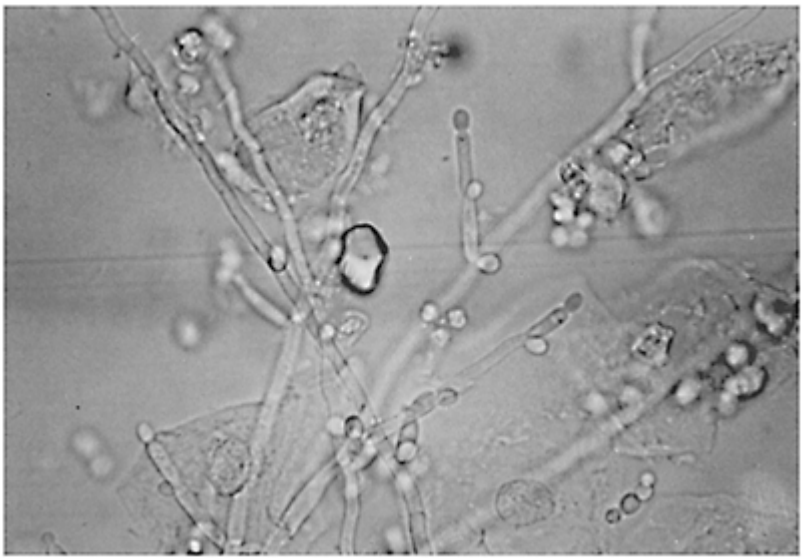

Figure 70.3 High power magnification revealing spores and pseudohyphae of *Candida albicans*

Stained smears

Stained smears of vaginal secretions are only occasionally required for the differential diagnosis of vaginitis and discharge because an accurate diagnosis can usually be made by correlating clinical findings with KOH/wet mounts. For those unfamiliar with the clue cells of *G. vaginalis*, however, the Gram-stained smear is very useful for identifying the short Gram-negative bacillus, which usually outnumbers all other organisms by at least 100 to 1. Dunkelburg, when examining several hundred slides from my files of patients with or without vaginitis, identified *G. vaginalis* on every slide taken from patients with the infection. He did, however, over-diagnose *G. vaginalis* in a small percentage of cases when small diphtheroids were the predominant organism. The stained smear is a more sensitive method for identifying candidal spores and filaments, but is of limited value for the diagnosis of trichomoniasis. Stained smears of vaginal secretions are extraordinarily useful, particularly in those cases where some difficulty is encountered in diagnosing the vaginal discharge, and in those cases with recurrent discharge as the presenting complaint. The use of Gram staining and Dif-Quick stain enables one to identify processes that have usually only been diagnosable after extensive laboratory culturing.

Gram staining makes the diagnosis of clue cells, lactobacillus overgrowth syndrome, and yeast infections (particularly in the non-mycelial phases) extremely easy. The technique for making a Gram stain is outlined inTable70.3.

The use of Dif-Quick, or Giemsa's stain usually enables the flagella to be seen. If, after examining the two basic wet smears, you make no appropriate diagnosis, prepare a Gram stain. This step is extremely useful when you are trying to determine the cause of recurrent

Table 70.3 Technique for preparation of Gram stain

Heat slide briefly
Cover with gentian violet (10 seconds)
Wash
Cover with Gram's iodine (10 seconds)
Wash
Decolorize with acetone/alcohol (immediately)
Cover with safranin (10 seconds)
Wash
Place cover slip on wet, stained surface and examine
Drop saline on the coverslip and re-examine with 100× objective

vaginitis. Heat the slide with a match or alcohol lamp until the material is almost dry. Then, examine the stained material under low- and high-power. First look for clue cells, which will be easy to recognize on Gram stain. Then look for polymorphonuclear leukocytes, hyphae, buds, other bacteria, and trichomonads. Trichomonads, admittedly, are hard to diagnose with Gram stain. The flagella do not retain color and the protozoa themselves stain only slightly. You have to look for the characteristic central nucleus centromere.

If you are dealing with a situation in which the discharge has dried or the trichomonads are non-motile, the use of Dif-Quick stain will enable the flagella to be seen clearly. Additionally, the use of Gram-staining allows you to use the oil immersion lens to examine the preparation at 1000×power or higher. With wet fresh Gram-stained material, you do not need oil to examine the slide because there is a water interface between the slide and the cover slip. All you have to do to get a clear view of the vaginal discharge is to place a drop or two of saline solution between the cover slip and the lens.

Experience in my office laboratory is that gonorrhea can usually be diagnosed by examining Gram-stained material from the endocervix and urethra. Reportedly, however, gram-staining has an overall accuracy of less than 50%, and the consensus is that it is particularly unreliable for the diagnosis of asymptomatic gonorrhea; with this, there can be no disagreement. Gram-stained smears tend to be more often useful in confirming suspected gonorrhea than the literature suggests. Their accuracy depends on careful exudate collection and staining and examination by a capable, sleuthing technologist.

Gram-stained smears, when immediately examined and found to be positive, can provide a 24-hour head start in the treatment of gonorrhea.

In an attempt to help clinicians, pathologists are increasingly reporting (with moderate accuracy) the presence of trichomonads, *G. vaginalis*, candida spores and filaments, and herpesvirus giant cells on the Papanicolaou smear. In general, cervicovaginal smears have not proved reliable for the differential diagnosis of vaginitis, and besides, the method was not designed for that purpose. False-positive and false-negative reports of trichomonads are made only too often. On the other hand, giant cells and intranuclear inclusion bodies seen in the cytological smear offer strong evidence of herpes genitalis and, when they are found with characteristic gross lesions, essentially clinch the diagnosis. Except for the confirmation of herpes genitalis, Papanicolaou smears are rarely indicated for the diagnosis of specific vaginitides.

Cultures

Clinicians are prone to place too much confidence in microbiologic cultures. In most clinical laboratories, microbiology is not the exacting science some consider it to be. Besides, cultures are only occasionally required in the differential diagnosis of vaginitis. In my practice, their use is primarily reserved to satisfy investigative protocols or to identify sexually transmitted disease (STD) pathogens.

Routine bacterial cultures as performed in many clinical laboratories are rarely informative for the differential diagnosis of vaginitis. The cultural isolation of a bacterium, even though it might be the predominant agent isolated, does not prove an etiologic relationship between that bacterium and the discharge or vaginitis present. Clinicians must guard against always assigning etiologic significance to bacterial agents enumerated on a laboratory report. For cultures to be useful at all, there must be good communication between clinician and microbiologist. Too few clinical laboratories are geared to provide useful answers to gynecologists; most utilize only routine culture media. The microbiologist should be furnished with two air-dried smears, and he should be given basic information about the problem.

Bacterial quantification has been used by urologists for many years, but has been conspicuously ignored by gynecologists. Many studies have shown that, qualitatively, essentially the same bacteria can be recovered from patients without vaginitis, yet these same studies often fail to mention the relative numbers of each bacterium present. The ratio of two types can vary as much as a thousand-fold in either direction.

To be sure, the colony count method can be misleading and difficult to interpret. The time of specimen collection, the transport medium, the interval between collection and media transplantation, the media used, the room temperature, and many other variables make quantification of vaginal bacteria difficult.

Gardnerella vaginalis

Several excellent culture media for the isolation of the bacillus have been employed. As a transport media, we have found Casman's broth with 5% rabbit serum highly satisfactory, and for primary isolations we still use Casman's blood agar with 5% defibrinated rabbit blood. The colonies on this medium are characteristic but minute and difficult to see with

the naked eye. Oblique lighting and use of a dissecting microscope are helpful. Dunkelburg prefers a media which he developed and calls PSD (peptone-starch-dextrose). The colonizing morphology with this medium is different from that on Casman's blood agar plates. Greenwood and Pickett developed a media using human blood which they called 'vaginalis agar'. Their experience suggests that this media has a distinct advantage over most others in use. The organism, being a facultative anaerobe, grows best in an atmosphere of reduced oxygen and increased carbon dioxide as is furnished by a candle jar. For practical purposes, the need for cultures is obviated by a careful correlation between clinical and microscopic findings.

Candida species

Candida species can be readily identified on a number of media. When available in screw-capped bottles or vials, they do not require an incubator to support growth, but growth is faster if an incubator is used.

As previously stated, KOH smear provides an immediate answer in most cases. A positive smear showing spores and filamentous forms obviates the need for a culture. Because candida is a commensal organism, often present without clinical disease, a negative smear with a positive culture does not necessarily mean that the patient has clinical candidiasis.

The KOH smear produces an immediate answer in most cases where mycelial formation has taken place. In those women in whom candidiasis is suspected, Gram staining may reveal numerous spores; however, there are a number of patients who have low grade vaginal symptoms with minimal discharge that on culture turn out to have a significant number of candida. It is suggested that in patients with normal pH with recurrent vaginitis, an odorless discharge and essentially no leukocytes present, a culture is made on suitable media.

Trichomonas vaginalis

A culture can provide a highly accurate way to isolate the trichomonad from a vaginal specimen, particularly when the culturing technique has been mastered, as in a research laboratory. Nevertheless, for reasons not always identifiable, trichomonas cultures performed by most clinical laboratories or in physicians' offices do not approach the accuracy provided by a careful examination of a properly prepared physiologic saline wet mount. We have had good luck using the Kupferburg simplified trypicase serum (STS) culture medium, incubated at 37ºC for 2–3 days. This media already contains human serum, providing essential growth factors as well as antibiotics for inhibition of bacterial growth. The Wittington-Fineburg media has also proved satisfactory.

TRICHOMONAS VAGINALIS VULVOVAGINITIS

Discharge is the cardinal symptom of this disease, but practically all women harboring the organism have, have had, or will have irritative symptoms such as itching, burning and dyspareunia. The color, and inflammatory changes seen by the clinician, are

dependent on the virulence of the strain. Pure trichomonad colonizations with a high virulence strain are the ones that usually present with frothy yellow discharge. Chafing, associated with malodorous discharge, practically clinches the diagnosis of trichomoniasis. Interestingly, only about 50% of patients yielding trichomonads complain of irritation at the time the organisms are first discovered. Urinary problems are reported by some patients with trichomoniasis. Urethrocystitis, caused by trichomonas infection, is occasionally seen in patients with or without apparent vaginal infection, In other words, a mild, abacteriuric pyuria seen with trichomonads in a cleanvoided or catheterized specimen can sometimes be attributed to the organism. An immediate disappearance of a persistent, mild pyuria in such a patient upon administration of metronidazole strongly suggests she had trichomonal urethrocystitis.

Vulvar signs

An analysis of a large number of my case records revealed that only 40% of patients with trichomoniasis showed evidence of gross tissue changes of the vulva at the time of the initial examination. There is usually only a mild erythema present and occasionally some edema. From the same analysis, we learned that only 30% of patients who yielded trichomonads displayed gross abnormalities of the vaginal mucosa. Profuse redness of the vagina was the usual sign seen in patients with acute infection. I should also point out that fewer than 10% of patients with trichomoniasis showed the ‘strawberry vagina’ that results from swollen papillae projecting through vaginal secretions. Fewer than 10% of the patients produced frothy vaginal secretions, and less than 10% had truly greenish discharges. The majority of trichomonal discharges are indeed gray, and often indistinguishable from the discharge of *G. vaginalis* vaginitis except by laboratory methods. Medical literature has too long perpetuated the idea that trichomoniasis is practically always associated with a greenish, frothy discharge and a strawberry vagina.

An occasional patient with trichomoniasis has a relatively dry vagina with pseudomembrane formation. In fact, some examples are suggestive of the thrush patches of candidiasis. Most cases of vaginitis emphysematosa, that is, vaginitis with cystoid spaces filled with gas and lying within the vaginal mucosa, are attributed to trichomoniasis. A few are caused by *G. vaginalis* vaginitis.

Diagnosis

Any patient of childbearing age with a vaginal pH of 5.0 or higher who also has pruritus is likely to have trichomoniasis. Because of its simplicity and accuracy, the microscopic examination of a wet mount preparation using physiologic saline is the laboratory diagnostic method of choice. Identifying actively motile organisms poses no problem; essentially immotile, rounded or ‘balled-up’ organisms are often discernible only under the high-power objective. Dif-Quick staining technique often enables trichomonads to be identified easily even after the unstained specimen has been non-diagnostic. Such organisms are seen in urinary specimens, in some patients with asymptomatic disease, and occasionally in patients who have recently douched or used vaginal medicaments. An occasional patient is seen who has severe vaginitis, apparent acute trichomoniasis, but with no detectable trichomonads. This phenomenon apparently results from autotoxins

within the colony. Christian *et al.* observed this when studying trichomonads in tissue culture.

According to the severity of the infection, trichomoniasis may be classified as asymptomatic, chronic, or acute.

Asymptomatic trichomoniasis

Small numbers of living trichomonads, often balled-up, small, and essentially immotile, are sometimes seen in patients with a vaginal pH of 3.8–4.2 who have a lactobacilli-predominant vaginal flora and usually no clinical, bacteriologic or histologic signs of disease.

Chronic trichomoniasis

Patients without distinct, gross changes in the vulvar or vaginal tissues, yet whose vaginal secretions are abnormal in volume, odor, consistency, pH, and bacteriology, are considered to have chronic trichomoniasis, the most common variety. Irritation may or may not be present, and histologically, the vagina shows varying degrees of inflammation.

Acute trichomoniasis

Acute infection is characterized by malodorous vaginal discharge, gross tissue reactions of the vagina and vulva, and irritative symptoms, particularly pruritus. Edema and erythema of the vulva are common gross abnormalities. The vagina usually shows one of the following signs: generalized redness, swollen papillae, or ecchymosis. As in the chronic state, the vaginal flora is essentially devoid of lactobacilli and the vaginal pH is elevated. Acute inflammation of the vagina is seen upon histologic examination.

Treatment

Since the ‘discovery’ of lactobacilli, numerous authors have suggested or claimed that vaginitis, regardless of type, but particularly trichomoniasis, could be successfully controlled or cured by restoring the normal vaginal flora. The most frequently suggested method for doing this has been to instill commercially cultured strains of lactobacilli into the vagina. To illustrate the futility of such an attempt, one need only point out that practically every woman had a normal flora dominated by lactobacilli or, sometimes, diphtheroids (both acidific rods) before acquiring a vaginal infection. Also to be remembered is that subjects developing candidiasis continue with a normal vaginal flora. While the thesis of treating vaginitis by restoring a normal vaginal flora was an attractive one, it has not panned out in practice. Matching microbes, or pitting lactobacilli as the ‘good guys’ against the ‘bad guys,’ trichomonas or *G. vaginalis,* practically always ends up in a victory for the bad guys.

Trichomonas vaginalis and *G. vaginalis* alter the vaginal flora by altering the vaginal environment, making it unfavorable to the lactobacillus. Within a few days after trichomonads or *G. vaginalis* have been eliminated from the vagina by appropriate

therapy, the bacterial flora rapidly disappear after successful inoculation of the vagina with trichomonads or *G. vaginalis*.

The development of metronidazole has to be one of the significant discoveries in gynecology, even though trichomoniasis is not a killer. A number of drug regimens have been used and found to be successful. Dr. Gardner recommends 500 mg bid for 5 days, taken by both the patient and her consort. Other authors use a seven day regimen of 250 mg, 3–4 times a day. By using proper isolation methods, the organism can be recovered from over 80% of the consorts of infected women. Since a failure to isolate does not prove that the consort is free of the organism, I recommend treating male consorts without attempting isolation. Trichomonads in men are often difficult to demonstrate, but the treatment of their infection is simple, safe, and effective.

While most reports on 1 day regimens, that is, 2 g in a single dose or 1 g twice in one day, are extremely encouraging and have many obvious advantages, a safe conjecture might be that in the long run, it will prove considerably less effective than the 5 day regimen.

Trichomoniasis in men

To deny that men have symptomatic trichomoniasis would be contrary to the findings of many careful investigators. This is not to say that symptomatic trichomoniasis is as prevalent in men as it is in women; Teokharov found the same incidence of urogenital trichomoniasis in both sexes. We have been able to recover trichomonads from the urethras of the majority of male contacts. Fewer than 20% of men harboring the organism have symptoms; more have symptoms soon after first contact than subsequently. Coutts and others found trichomonads in 68% of men who had been diagnosed as having non-gonococcal urethritis. Rarely, the flaggelates identified in the vagina may represent Giardia transmitted from the rectum across the perineum.

Allegedly, trichomonads die out in the male urethra within a few weeks after the last contact with an infected woman, but this has not been a confirmed observation. LeDuc unequivocally stated ‘current opinion that trichomonas urethritis is self limited is an error. The concept that the parasites will spontaneously disappear from the urethra of the man who wears a protective sheath to avoid reinfection during coitus is untenable’.

BACTERIAL VAGINOSIS (BACTERIAL EXCESS SYNDROME)

Investigators have long known that the mere isolation of a predominant bacterium from the vagina does not necessarily prove a cause-and-effect relationship between that bacterium and the infection present.

The relationship of *G. vaginalis* to disease is not a simple cause-and-effect phenomenon. *G. vaginalis* is a common isolate from the female genital tract. The difference between colonization and disease appears to be a partial function of the magnitude of bacterial replication. Quantitative bacteriological studies have shown that disease, when due primarily to *G. vaginalis*, is associated with greater than 10^8 colony forming units (cfu) per gram of vaginal fluid. Different bacterial isolation patterns exist: *G. vaginalis* alone, *G.vaginalis* with a relatively limited bacterial flora, *G. vaginalis* as

part of an anaerobic polymicobial bacterial flora, and an anaerobic polymicrobial bacterial flora without *G. vaginalis*.

Pfeifer and associates and Chen and coworkers have hypothesized that a symbiotic relationship may exist between *G. vaginalis* and other vaginal bacteria (particularly anaerobes) in patients with culture proven *G. vaginalis* in bacterial vaginosis (BV). Several observations oppose the thesis. Classic disease can be induced from pure cultures of *G. vaginalis.* Some patients with the classic disease yield pure cultures of *G. vaginalis.* In these patients stained smears show that *G. vaginalis* usually outnumbers all other organisms 100 to 1. In other patients, anaerobes are recoverable. That other bacteria are necessary to produce the described disease seems probable in selected individuals.

Bacterial vaginosis appears to be an end-titration point for a number of bacterial combinations.

Demographically, BV appears to have at least two divergent patterns. In the first pattern, *G. vaginalis* is present as sole dominant isolate or present with a limited number of anaerobic bacteria. This pattern is prevalent in the private sector. The second subgroup is microbiologically characterized by a complex polymicrobial, bacterial flora, which may include *Streptococcus agalactiae, Escherichia coli, G. vaginalis, Peptostreptococcus* species, *Bacteroides* species, *Prevotella* species, *Mobiluncus* species, *Staphylococcus epidermidis, Enterococcus faecalis* and *Mycoplasma hominis*.

The suffix '-osis' translates to 'an excess of'. In the case of BV, the literal translation is 'an excess of bacterial vaginas'. Choice of the -osis was done to undeline the absence of inflammation associated with this disease entity'. Careful analysis has documented that within bacterial vaginosis there is a subgroup who have BV and whose demography, predilection for co-infecting STDs and response to therapy differs. Depending upon the population demographic characteristics, 30–40% of women with BV have '-itis'. Larrson *et al.* demonstrated vaginal leucocytosis in 36.5% of women with documented BV.

Symptoms

Discharge and ordor are the principal symptoms of BV. The discharge is characteristically a gray, homogenous, malodorous vaginal discharge. The odor is described as musty or fishy. While many women are acutely conscious of these symptoms from the very onset of the infection, other women do not volunteer complaints because their symptoms are so mild. However, many of these admit the necessity of frequent douching and notice a positive change when the *G. vaginalis* organisms have been successfully eradicated and the normal vaginal ecology restored. A husband is often conscious of his infected wife's unpleasant odor, a fact that can 'turn him off and make for an unhappy marital situation. Concomitant presence of pruritus or vaginal itching should alert the clinican to either co-infection or a mis-diagnosis.

Signs

Gross vulvitis and vaginitis are not characteristic of the disease. *G. vaginalis* is a surface organism that does not invade the vaginal wall or elaborate toxic substances that provoke reactions in the vulvovaginal epithelia. As a rule, histologic preparations show no more

of an inflammatory reaction than does normal vaginal tissue. Based on these facts, the legitimacy of the term vaginitis for this entity has been questioned.

G. vaginalis vaginitis produces a varying degree of discharge, from scanty to profuse; the *G. vaginalis* discharge is usually less abundant than the discharge in cases of acute trichomoniasis. The consistency of a *G. vaginalis* discharge is essentially the same as a trichomonal discharge; it resembles a thin flour paste, being turbid, homogeneous, and free of grossly visible clumps of epithelial cells that are seen in normal vaginal secretions. In about 95% of the cases, the discharge is gray. Its fishy odor, less offensive than that in the usual case of trichomoniasis, is characteristic and of diagnostic value. Frothiness of the discharge is apparent in about 7% of the cases, but is usually minimal, consisting of only small bubbles. Nevertheless, frothiness should never be considered a diagnostic sign exclusive to trichomoniasis, an error long perpetuated in the literature.

The pH of the discharge is practically always between 4.7 and 5.5. Patients of childbearing age who have vaginal secretions of 5.0 or higher, and do not have trichomonads in the vagina, may have an abnormal vaginal flora.

Diagnosis

Traditionally, the diagnosis of BV has been contingent on clinical and wet mount findings of the following:

(1) a profuse grey-white discharge;
(2) the presence of ‘clue cells’;
(3) demonstrate of profuse bacterial overgrowth by coccobacilli (100 to 1 ratio to other bacterial forms);
(4) a pH greater than 4.5; and
(5) an absence of white blood cells.

The advocacy of the Gram stain as the ultimate diagnostic determinant has introduced a compounding variable which has resulted in the fusion of somewhat diverging forms of the disease. Women with leukocytosis and whose analysis of bacterial morphology does not exhibit the characteristic coccobacillus predominance to any other bacterial form appear to represent a significant subset of patients who are at high-risk for co- or prior infection with other STD pathogens.

The role of *Gardnerella vaginalis*

The fusion of two wet mount patterns whose pathogenesis appers to differ into a single entity, has brought into question the role of *G. vaginalis* as a pathogen. Below is listed the original argument of Herman Gardner.

(1) *Gardnerella vaginalis* is the predominant organism in the vaginas of patients with the described vaginitis;
(2) the organism is the only one consistently isolated from the vaginas of patients;
(3) the organism is rarely isolated from patients who do not show clinical signs of the disease;
(4) the characteristic signs and laboratory findings disappear abruptly upon eradication of *G. vaginalis* from the vagina and reappear upon reinfection with *G. vaginalis;* and

(5) experimentally, we successfully inoculated disease-free vaginas with material from the vaginas of patients with proven *G. vaginalis* vaginitis and reproduced disease.

In each instance, a culture of the donor material yielded *G. vaginalis* in pure culture or as the predominant bacterial agent. The recipient subjects were not only free of all clinical signs of vaginal disease on the day of inoculation, but their vaginal flora consisted predominately of lactobacilli. Of 15 normal patients inoculated with the infectious vaginal material, 11 developed the clinical disease within 10 days, and *G. vaginalis* became the predominant organism in all 11 vaginas. These induced infections persisted indefinitely in the majority of the subjects.

Bacterial vaginosis as a sexually transmitted disease

In some, but not all women, BV conforms to the risk factors characteristic of STD. Berger *et al.* studied homosexual women who sought gynecologic care at a community center and in a private gynecological clinic. Of 11 index women who had BV, eight (72.2%) had partners who also had BV. The likelihood of a female partner having BV was 19.7 times greater, if the index women had BV.

In the Swedish Women's Health Study, Nilsson *et al.* compared risk factors associated with BV and *Chlamydia trachomatis* infection. No significant differences in sexual activity risk factors existed when women with BV were compared to those with chlamydial infection except for a higher frequency of casual sex. Larsson *et al.* studied 400 women with and 400 women without BV. Women with BV had a higher number of lifetime sexual partners and exhibited behavior similar to women at risk for STDs.

When the issue of documented, concomitant co-infection is analyzed a significant portion of women with BV can be demonstrated to have one or more major STDs. Tchoudomirova *et al.* found that 37.8% of women attending STDs clinics had BV and were frequently coinfected. In their study, BV correlated with age younger than 25 years, lack of a permanent sexual partner, use of the intrauterine device (IUD) other STDs and smoking. Joesoef *et al.* identified a 23.3% prevalence of major STD among pregnant women with BV. Peters *et al.* similarly found the presence of BV to be significantly associated with the number of cigarettes smoked per day, age at first intercourse, the lifetime number of sexual partners and current *C. trachomatis* infection.

Bacterial vaginosis and pelvic inflammatory disease, ectopic pregnancy and secondary infertility

A number of static group comparisons have suggested an etiological connection between BV and a number of disease entities ranging from acute salpingitis to acquisition of retrovirus infection. Spiegel has proposed that BV or the organisms associated with BV are associated with adverse outcomes of pregnancy, including premature rupture of membranes, chorioamnionitis, fetal loss, postpartum endometritis, cuff cellulitis, and upper genital tract disease. There is no question that women with acute salpingitis, ectopic pregnancy, or secondary infertility are more likely than not to have or have had BV; however, one is hard pressed to explain how a noninflammatory process produced disease comparable to *C. trachomatis* and/or *Neisseria gonorrhoeae*. Bacteria in volved with polymicrobial BV can be the same bacteria which can function in the anaerobic

progression. In the case of upper tract genital infections, a major STD pathogen usually functions as the initiator of disease.

Treatment

The monolithic conceptualization of clinical BV has precluded development of optimal therapeutic efficacy. The current drugs of primary utilization are either per oral or intravaginal metronidazole or clindamycin. The relative effiacy of antibiotics which address the anaerobic constituency of the vaginal bacterial flora lend credence to the concept that eradication of the major anaerobic bacteria tends to abort the disease process. With thes drugs, short-term clinical cures can be achieved in 75% to 85% of the cases. Microbiological cures rarely achieve such percentages. If monitoring is extended to four weeks and beyond, the abnormal bacteria reappear in approximately a third of the previous microbiological cures.

The reasons for both therapeutic failures, and to a lesser extent therapeutic successes, have not been well delineated. One of the factors contributing to the former is the fact that individual *G. vaginalis* isolates are resistant to metronidazole.

Where the 'BV flora' differs from the characteristic anaerobic progression is the common occurrence of *Mobiluncus* species. The prevalence of *Mobiluncus* species within polymicrobial BV varies within the population groups sampled. Royce *et al.* demonstrated that *Mobiluncus* species was present in 12% of black gravidas with BV as compared 1.3% of white gravidas with BV. Quantitatively, 73% of blacks, compared with 40% of white gravidas had high level replication. *Mobiluncus* species are resistant to metronidazole. Depending on whether one is dealing with *M. curtisii* or *M. mulieris*, sensitivity to erythromycin and clindamycin differs. The adequacy of Gram stain alone for the diagnosis of *Mobiluncus* species may be a problem. Burns *et al.* analyzed 299 vaginal swabs by Gram stain and by culture. *Mobiluncus* species were identified in 8.4% of specimens by Gram stain, but only 0.7% by culture.

The European physicans have addressed the problems of antibiotic resistance and bacterial complexity by the use of combined use of metronidazole and erythromycin.

In the last several years, we have seen an almost complete reversal of the position advocated in the last edition of this text. It is still true that metronidazole, given orally, either as a single 2 g dose or over 7–10 days, 2–3 times a day, using 250 or 500 mg per dose, has been identified with highly successful cure rates. On the other hand, the oral treatment also is frequently followed by a variety of mild to severe side effects. Currently, the use of either clindamycin or metronidazole vaginal cream for a week has resulted in more or less the same cure rate, but with far fewer side effects. Initially topically applied agents provided an unpredictable therapeutic response and have thus been largely abandoned. In recent years, we have resorted mainly to orally administered systemic agents. Metronidazole has proved to be the most effective agent available.

The question of whether or not to treat women who are unaware of the infection has arisen. Patients who have a habit of frequently douching, and perhaps those habituated to their own odors, are unlikely to complain and seek treatment. Possibly, patients unaware of the disease should be allowed to continue in ignorance if cooperation between them and their consorts is likely to be difficult. However, it should be recognized that even

though the woman is unaware of the infection, her consort may be only too conscious of her unpleasant odor.

Since *G. vaginalis* may be sexually transmitted, a woman's sexual consort should be considered and logically treated with the same systemic agent. A difficult therapeutic challenge often develops when a third party or multiple sexual partners are involved.

Any women with BV should be thoroughly evaluated for co-infection with major STDs.

VULVOVAGINAL CANDIDIASIS

In four widely spaced studies in my office practice, employing essentially the same laboratory methods and clinical interpretations, I found the following prevalence rates for vulvovaginal candidiasis in gynecologic patients: 1944, 2.8%; 1957, 4.3%; 1964, 5.9%, and 1976, 10.1%.

A few years ago, in doing differential cultures on 100 consecutive patients with candidiasis, Dr. C.D. Dukes and I found that only 67% of the infections were due to *Candida albicans*, while the balance was due to *C. tropicalis*, *C. pseudotropicalis*, *C. stellatoidea*, *C. krusei*, and *C. quillermondi*. These findings are probably only of academic interest since there was no discernible difference in the clinical features of the infections caused by the different species. The published reports of Carter *et al.* and many others should dispel any thought that *C. albicans* is the only pathogenic species.

We also found acidific rods (lactobacilli and diphtheroids) to be the predominant vaginal bacteria in patients with candidiasis who yielded no other vaginal pathogens. This should be no surprise to anyone, as Doderlein, in his historic treatise published in 1892, reported an association between large Gram-positive rods and fungi, and stated that the acid medium of the vagina favored both. *G. vaginalis* and *Candida* are not uncommonly associated, with *G. vaginalis* producing an elevated pH and odor and with *Candida* causing pruritus.

Source of *Candida*

Candida can be recovered from almost any area of the body. It is found in the oral cavity and intestinal tract in a high percentage of women yielding vaginal organisms. Candidiasis is not considered a venereal disease, but certainly men can sexually transfer the organisms from one woman to another; a man with candidal balinitis can also implant the organisms to cause infection.

Predisposing factors

According to the evidence, host factors controlling susceptibility are much more important to the development of candidiasis than the chance vaginal contamination with a candidal species. Pregnancy is the most important predisposing factor. Most clinicians feel that 'pseudopregnancy' from contraceptive pills increases the incidence and intensity of the disease. Some of the reasons suggested for this increased susceptibility are:

(1) increased vaginal glycogen from estrogens;

(2) vaginal thinning from progestational agents;
(3) altered sugar metabolism; and
(4) altered sexual habits.

The wide use of antibiotics has produced the greatest increase in candidiasis. Regardless of the exact mode of action, antibiotics play a dual role by increasing candidal colonization by the host and by inducing rapid multiplication of vaginal *Candida*. The prevailing opinion is that the antibiotics knock out bacterial competition, leaving the door wide open for *Candida*. Investigators have found other explanations for the effects of antibiotics, including a reduction in phagocytosis of *Candida,* a reduction of antibodies to *Candida,* and a direct stimulatory effect on *Candida*.

Perhaps of more long range importance than the antibiotic's precipitation of individual attacks is the increased *Candida* colonization of the host, particularly in the intestinal tract, where, according to Lon and Baker, *Candida* may be increased a thousand-fold. This colonization is long-lasting and serves as a continual source of vaginal reinfection.

Diabetes mellitus, while a strongly predisposing factor when present, is of little significance to the overall picture of this disease. Most patients with chronic, recurrent candidiasis do not have diabetes or an altered glucose tolerance. However, it can be said that practically all premenarchal and postmenopausal subjects who develop candidiasis either are taking estrogens, have recently taken antibiotics, or have diabetes.

There must be an 'X factor' to explain the increased susceptibility of many individuals. It may be related to antibody titers against candida species. Some patients with the chronic recurrent disease have lower antibody titers to *Candida*. In growing candida in blood from patients with candidiasis, Lourie and Brayton learned that the patients' sera exhibited diminished candidicidal activity. Increased susceptibility of the vulvar tissues to allergenic or endotoxic substances produced by *Candida* may explain some examples of apparently reduced resistance. An occasional patient with severe tissue reactions yields a minimal number of organisms, whereas a patient may have a vagina full of thrush patches without signs or symptoms of irritation. It is important to recognize that many patients with recurrent candidiasis have an addiction to high-sugar containing products such as chocolate. This seems to be accentuated just before the onset of the menstrual period and is almost at the level of a severe compulsion or addiction. If the sugar habit cannot be reduced, it is extremely difficult to eliminate candidiasis for any length of time.

Treatment

Most recurrent infections are autogenous reinfections. The elimination of the organism from the vagina poses no problem, but the discovery and elimination of infectious foci and predisposing factors are where the difficulty lies. For the patient with chronic recurrent disease, I recommend one or more of the following:

(1) longer therapy not interrupted during menstruation;
(2) use of an intravaginal candidicide nightly for a few days after each menstrual period as a prophylactic measure;
(3) use of an intravaginal candidicide during and for several days after any course of antibiotic therapy;

(4) discontinuation of oral contraceptives; and
(5) application of nystatin ointment or one of the azole preparations to the patient's preputial folds and to her consort's penis twice daily for 10 days.

Despite all of the appropriate treatment measures, many women have recurrent or persistent yeast infections. Careful histories are taken. It can be seen that these women have more difficulties with *Candida* infections that often go beyond local vaginal infection and that the recurrences may be only the tip of the iceberg. The 'marker' symptoms that characterize these women are:

(1) extraordinary addiction to sugar. This unfortunate habit provides a substrate for yeast growth that enables them to multiply rapidly wherever they are located in the body;
(2) bloating and flatulence produced by yeast multiplying in the gastrointestinal tract; and
(3) other yeast related symptoms that are beginning to be described in the medical literature, such as autoimmune disorders, premenstrual syndrome, depression, arthritis, cold intolerance, and cystitis.

These disorders appear to be produced by a systemic response to yeast toxins and/or antigens produced in the gastrointestinal tract by some of the more potent strains of *Candida*. Reduced immunity to candida may result in colonization in the urethra, bladder, sinuses, gums, bronchi, esophagus, or other mucous membranes. The usual patient with recurrent vaginal candidiasis who has a gastrointestinal reservoir will require 4–6 weeks of oral nysatin therapy at which point there may be rehabilitation of the body's immune defense system. These recurrent infections related to immune defense problems are extremely complicated to manage and require prolonged and diligent therapy to eradicate the foci of the yeast infection and restore capability to the immune defense system.

One other important caveat needs to be observed, that women being treated for yeast infections frequently develop lactobacillus overgrowth syndrome (which will be described in the next section). This pasty, white discharge is frequently misdiagnosed as being a *Candida* recurrence. This results in an erroneous diagnosis made over the telephone.

Therapy is frequently ordered without a diagnosis being made. Anticandidal therapy does not cure lactobacillus overgrowth syndrome or its symptoms. It is important that the discharge be actually diagnosed in the office or the patient be supplied with culture media to culture her discharge at home. Self-culturing is a simple procedure using only sterile applicator sticks and culture media (which can be purchased for approximately one dollar a tube and then supplied to the patient for her use). I cannot emphasize too highly the importance of actually verifying yeast recurrence in women to prevent erroneous therapy.

Diabetic vulvovaginitis

Diabetic vulvovaginitis is primarily related to chronic candidiasis rather than to an irritative tissue response to abnormal metabolites in the diabetic's urine. Classic diabetic vulvitis results from a combination of chronic candidiasis and trauma from rubbing and scratching for the relief of pruritus. Simply controlling the patient's diabetes does not result in cure or control of this condition. Even controlling the diabetes and eliminating all *Candida* organisms does not cure the long-neglected patient. These patients usually have developed a severe lichen simplex chronicus resulting from the scratch-itch reflex.

They require not only control of the diabetes and the elimination of *Candida*, but also prolonged use of topically applied corticosteroids for controlling pruritus. Even though all three approaches are required, it sometimes takes months to achieve patient relief; some vulvar tissues are never restored to normal.

An interesting observation is the occasional finding of a microscopic diagnosis of vulvar 'leukoplakia' (more correctly called hyperplastic dystrophy) in patients with diabetes. The irritative effects of candida or vulvar tissue and the effects of physical trauma from scratching provoke hyperkeratosis, epithelial hyperplasia, and the inflammatory infiltration, the chief components of hyperplastic dystrophy.

Primary cutaneous candidiasis

Primary cutaneous candidiasis of the vulva is an infection of increasing incidence and its development is favored by warm, humid climates in which maceration and other changes in the skin provide a good environment for fungus growth. The lesions have usually reached a large size when first observed, and they tend to be beefy red, weeping, and with rather precisely defined scalloped edges. The majority are associated with small, discrete satellite lesions which offer a clue to diagnosis. Histologic section of these satellite lesions shows them to be vesicopustules limited to the superficial epidermis. The lesions of this infection are usually easily distinguished from those of tinea cruris since the lesions of the latter spread peripherally with an active vesiculated leading edge and with central clearing. Scrapings from candidal lesions yield both spores and filaments, while those of tinea show filamentous forms only. Primary vulvar cutaneous candidiasis is occasionally present without associated vaginal infection. I have observed patients with the cutaneous disease but with negative vaginal candidal cultures.

In treatment, one or two applications of gentian violet afford rapid relief. This is then followed by the application of the azole cream two or three times daily for a minimum of two weeks. Vaginal medications are used simultaneously. Oral antifungal drugs may be required. Although gentian violet is quite efficacious it is well known to stain everything, making it very unpopular with patients. The availability of over-the-counter clotrimazole and miconazole vaginal preparations has resulted in a veritable explosion in the self-treatment of suspected vaginal candidasis. Estimates of incorrect self diagnosis range as high as 50–75%. The biazole preparations reputed to have the highest potency against various species of *Candidia*, particularly the non-albicans variety, are the terconazole creams or inserts. In cases of recurrent candidiasis, the daily frequency and length of treatment may have to be doubled or tripled. Oral single 150 mg dose fluoconazole has been approved as a treatment for acute candidiasis. However, in actual practice, especially with recurrent candidiasis, it may require 7–30 days of treatment to eradicate an invasive highly pathogenic yeast. Itraconazole, or ketoconazole are also useful for orally treating candidiasis though the package insert is not labelled for this indication. Several authors have found capsules containing 600 mg of boric acid to be useful, especially for non-albicans candidiasis.

CANDIDA (TORULOPSIS) *GLABRATA* VULVOVAGINITIS

Candida glabrata has been an obscure organism, so much so that little mention is made of it in texts of medical mycology. I agree with Wickerham, Kerns, and Gray and Perju *et al.*, that it is a marginal or weak pathogen capable of producing mild vulvovaginitis in susceptible subjects. The organism can also be present without inciting irritative signs and symptoms.

Clinical features

The chief clinical feature of infection is a vaginal secretion that resembles a normal secretion, but is more fluid. The secretion is white or slate-colored and is not malodorous. Thrush patches do not form. Vaginal activity is within the range of pH 4.0–5.0 in contrast to the 3.8–4.2 pH range of normal secretions. Irritative signs such as erythema are only slight, if present at all. The patient may complain of a discharge and mild irritative signs and symptoms such as itching and burning.

Diagnosis

Any patient having an increased vaginal secretion with mild irritative signs and symptoms of vulvovaginitis, but whose secretions yield none of the usual vaginal pathogens, might be suspected of having *C. glabrata* infection. Both wet mount preparations and stained smears reveal tremendous numbers of spores similar to those of *Candida,* though highly variable in size and without associated hyphae. The presence of *C. glabrata* can be confirmed by culture.

Treatment

The most effective therapeutic agent for *C. glabrata* vaginitis has not been determined. Most preparations used for candidiasis are successful but only if used long enough. Triazoles and/or boric acid capsules have been successfully used.

LACTOBACILLI OVERGROWTH SYNDROME

This syndrome is characterized by a pasty discharge with no evidence of vaginal irritation or odor but with low-grade burning or discomfort that is greatly increased after sexual activity. Table 70.2 gives the key diagnostic points.

The smear is characterized by many rod-like organisms of varying lengths, stripped nuclei, cytoplasmic debris, and large numbers of epithelial cells. Few other bacteria or yeast are found on the Gram stain. Cultures are always reported as ‘normal vaginal flora’ or ‘lactobacilli’.

This condition arises in women who have been treated several times (or more) for vaginal discharges with an assortment of antibacterial and antifungal medications. The

lactobacilli become the dominant vaginal microorganism. It is possible that the irritative form of

Table 70.4 Chemical irritants

Deodorant soap	Home remedies
Perfume	Deodorant sanitary napkins or tampons
Chemically treated toilet paper	Chemically treated permapress clothing Talcum powder
Deodorant sprays	Bubble baths
Spermicides	Chemically treated swimming pool water
Douches	Hot tubs or jacuzzis
Laundry detergent	Over-the-counter medicaments
Shampoo	Adhesive backed sanitary pads

overgrowth contains lactobacilli that are more virulent than the usual ones found in the vagina. They certainly seem capable of breaking down the vaginal mucosa by producing enough acid to lyse the cytoplasm and strip the nuclei free of the cell.

The Drs. Cibley recommend baking soda douches (1 or 2 tablespoons to a quart of warm water) to raise the vaginal pH. This remedy is effective if carried out for a considerable length of time, and if no intervening antimicrobial or vaginal therapy is interposed. The aim of therapy is to restore the usual vaginal microflora, and to reduce the excess of lactic acid being secreted.

UNDIAGNOSED VAGINOSIS

The most puzzling form of vaginitis to be encountered is a vaginitis in which no identifiable pathogen can be located. In many cases, these infections are found in women who have had recurring problems and have had recurring multiple treatments, suggesting that the organisms are survivors of previous therapy (i.e. antibiotic-resistant organisms). In general, the discharge is profuse, thin, non-odorous, and slightly discolored. These vaginitides are divided into two classes: in one, there is profuse leukocytosis with mixed bacterial overgrowth. Try to avoid the use of systemic antibiotics since these are almost always seen as reinfections, and there is some trepidation about further developing antibioticresistant strains. If the organisms appear to be primarily Gram-positive, use povidone iodine solution at much higher strengths than is normally recommended (one ounce per pint of douche solution). If the organisms are primarily Gram-negative, hydrogen peroxide douches (approximately 2 ounces to the pint) may be tried.

Table 70.5 Mechanical irritants

Condoms	Diaphragms
Cervical caps	Tampons, especially with plastic applicators

Vibrators	
Dildoes	Other vaginal foreign bodies
Frequent and/or vigorous genital manipulation	Occlusive, non-porous undergarments Tight crotch-hugging jeans
Exercise suits	Horseback riding
Exercise bicycles, etc.	

Since there are no antibiotic sensitivity studies generally available (or even indeed confirming cultures), the entire management of these cases is based on educated guesses. If there is any suggestion (by the presence of other problems) of impaired immunity, then the patient should be given a program for improving her general health that includes increased rest, stress reduction exercises, sunlight, improved nutrition, vitamin and mineral supplementation, and essential fatty acid therapy.

The second type of infection is characterized by profuse leukorrhea without any signs of bacterial overgrowth. Here an assumption is made that these represent contact vaginitis or an allergic reaction. In such cases, efforts are redoubled to locate a contact irritant. This search may be rewarded by the discovery of the use of a product such as talcum powder or deodorant sanitary napkins, that might be the inciting agent. For these contact reactions, non-irritating irrigation douches, such as one or more tablespoons of baking soda to a quart of warm water, is one of the cornerstones of the treatment. A list of possible contact irritants or mechanical irritants is seen in Tables 70.4 and 70.5.

VIRAL VAGINITIS

It is difficult to ascribe a role to the presence of either human papilloma virus (HPV), herpes virus, or other viruses in the development of leukorrhea and/or vaginal irritation. Since essentially no specific vaginal lesions have been noted with herpetic infections and the cervical lesions appear not to be associated with profuse discharge, it might be assumed that the herpes viral family is not involved. Papilloma virus, however, is a real problem. Coppleson has described the diagnosis of subclinical vaginal HPV infections. Elongated vaginal papillae can be seen with the naked eye but are better assessed using the colposcope. The Seattle group calls these ‘asperites’. Each of these projections contains a central capillary can be seen with the naked eye but is much clearer when a colposcope is used. A confirmatory diagnosis based on vaginal biopsy reveals koilocytosis. These appear to be found with some degree of frequency in women who have been treated for multiple vaginal problems, generally unassociated with discharge, with essentially negative microbiologic findings. In these women, the chief complaints are related to discomfort after coitus, persistent pain or burning. Once the diagnosis is made, treatment depends on the extent of the lesions. There is currently no labelled preparation to use for vaginal HPV. Some clinicians have used 0.5% podofiloz gel or solution for this purpose. Imiquimod cream 5% has not been evaluated or labeled for mucosal use. However, it would appear to be relatively safe for such indications compared to the older and quite destructive therapies such as 5-fluorouracil.

PERSISTENT VAGINITIS

If vaginitis persists after having made a specific diagnosis, one has to go back over the initial diagnostic and therapeutic process.

Diagnostic errors

It is almost self-evident that if an accurate diagnosis was not made to begin with, then effective treatment is not possible (Table 70.6). As you look at the causes, however, you realize that one of the problems may be that only a single one of a group of multiple pathogens was identified at first, and hence, only one of the etiologic agents was treated. If the lesion has persisted (aside from the problems with erroneous diagnosis due to inadequate examination of the vaginal discharge), one then has to examine the cervix more carefully to see if there is a source of infection located within the cervical canal. Certainly, if cervicitis is considered to be present, a chlamydial infection will have to be ruled out. The urethra may also be the origin of what was originally thought to be a vaginal discharge and irritation. Again, urethral massage and culturing should serve to clarify this particular problem.

One of the major causes of persistent infection is related to the presence of the infecting agent within the fecal stream, whether this be persisting candidiasis, giardiasis, pinworms or bacteria. The ultimate resolution of the problem will only occur when the fecal source is identified and the offending agent eliminated. Chemical and mechanical causes of vulvovaginitis must be identified and treated.

Treatment problems

The other major source of persistent infection has to do with inadequate treatment. It is quite possible that a too short drug regimen for the particular density or virulence of the infection was prescribed. Patient compliance is another frequent problem, as many patients stop therapy as soon as they feel better, or stop therapy because they are having unpleasant side-effects from the medication prescribed. Then, too, a number of organisms that are now present may have partial or complete resistance to drug therapy. Trichomoniasis has been described as occasionally being resistant to metronidazole. Hopefully, tinidazole and some of the other agents will become available in the United States in the event that a genuinely resistant trichomonad is encountered. For the moment (in the United States) we are restricted to increasing both the dose and the length of treatment in an effort to deal with the resistant organisms. *Gardnerella* vaginitis is getting to be more of a problem with each passing year. Since we have no microbiologic guidance from the laboratory, we are blindly committed to using metronidazole as a first therapy.

If Flagyl has failed even with the prolonged higher doses, amoebecides may be tried such as diodaquin.

Incorrect treatment

Another category of problem develops when the correct diagnosis was made but inappropriate therapy was prescribed. This may be due to a temporary mental lapse or fatigue on the part of the provider but nevertheless, the treatment was inappropriate. Thus metronidazole was prescribed for a non-gardnerella bacterial vaginitis. Worse yet, metronidazole may be prescribed for a recurrent yeast infection. Once the inappropriateness of

Table 70.6 Persistent vaginitis

- **A. Original diagnosis erroneous**
  1. Incorrect treatment prescribed
     - a. Diagnosis and treatment made over the telephone
     - b. Diagnosis made by ‘eyeballing’ discharge
     - c. Diagnosis made by wet smear only
     - d. Symptoms due to a mechanical or chemical irritation
     - e. Disease arises from a cervical, urethral, or anal source
     - f. No vulvovaginal pathology
       1. The complaints are psychosomatic
       2. Symptoms due to excess ovulatory mucus
       3. Discharge due to excess sexual lubrication (i.e. ‘hot pants’ syndrome)
- **B. Diagnosis cannot be made in office**
  1. Unidentified bacterial pathogens responsible
     - a. Mixed Gram-positive/Gram-negative microbial overgrowth
     - b. Mobiluncus (curved anaerobic rods)
     - c. Enterococci
     - d. Gram-positive micrococci
     - e. Other bacteria
  2. Fecal parasite/protozoa
     - a. Pinworm
     - b. Giardiasis
  3. Viral disease responsible
     - a. Papilloma virus
     - b. Herpes virus

4. Mycosis other than *Candida albicans* responsible
5. Other, as yet unidentified etiologic agents

C. Diagnosis correct

1. Treatment not adequate
   a. Dose too low
   b. Drug regimen too short
2. Non or partial patient compliance with treatment plan
   a. Treatment plan not followed
   b. Drug taken only until symptoms disappear
3. Organism (partially or completely) resistant to drug
4. Incorrect medication prescribed
5. Immune defense system impaired
6. Other sexual partners
   a. Infected partner not treated adequately—no barrier protection used
   b. Patient infected from a new sexual contact
   c. Partner infected from a new contact
7. Reinfection from anal, oral sex, digital, mechanical activity. Patient reinfected from continuing fecal contamination during the sex act, either heterosexual, homosexual, or autoerotic or from some pathogen present in the oral cavity

the therapy is recognized, you are on your way to a resolution of the problem.

RECURRENT VAGINITIS

Recurrent symptomatic bacterial problems can generally be handled reasonably well with the vaginal preparations of metronidazole, or clindamycin. While a large number of oral antibiotics are and have been used, their use is always fraught with possible long lasting effects such as necrotizing enterocolitis, prolonged gastrointestinal upsets, enteric candidiasis, and the developing of resistant organisms. Oral antibiotics should probably only be prescribed with concomitant use of oral nystatin (at least two million units per day) and potent *Lactobacillus acidophilus* (at least 5–10 billion/day). Recurrent vaginitis poses another set of problems completely. It is differentiated from persistent vaginitis by the presence of symptom free intervals with no trace of the original organisms apparently present in the vagina. Recurrent vaginitis implies that there had been, in fact, a complete microbiologic cure of the first infection. These problems are generally related to reinfection via sexual transmission or fecal soiling of the vagina.

It never fails to surprise me when I see a patient who has been treated by several gynecologists who have not attempted to find out if the sexual partner was infected.

There was apparently no thought about the sexual transmission of vulvovaginitis. Certainly, we are all aware that trichomoniasis, *Gardnerella* and candidiasis may be spread sexually. If the patient is married or in a steady monogamous relationship, efforts should be made to diagnose and treat the partner. At the very least, the patient should be advised that this can be a STD and that it would be prudent for her to avoid sex until the treatment program is completed. At the same time, a recommendation that her partner use condoms until such a time that the disease was completely eradicated should also be given.

However, when the disease has recurred, the issue of partners must be raised and pursued. As you might anticipate, this can be a very sensitive and touchy discussion. It is possible that the patient's consort might deny all symptoms, refuse all treatment (deny outside contact) and infer that the patient acquired the disease from some other person. Worse yet, if the partner had taken the suggested treatment and the condition recurred, suspicion might arise that there are other players in the game (i.e. does either partner have another partner?). We live in a new world as far as traditional relations are concerned. Monogamy may still be the norm but multiple sexual partners may be a component of your patient's life or patient's partner's life. In a form that is to be filled out for diagnosing recurrent vaginitis, these questions are raised. In addition to ascertaining the number of sexual players present at the time of the primary treatment, questions must be asked to see if any new partners are in the picture.

Moving beyond the question of numbers of partners, one must raise the issue as to the type of sex play that the patient engages in. Fecal contamination may be a prime source of reinfection. Engaging in anal intercourse followed by vaginal sex without any intervening cleansing, moving from anal digital stimulation to vaginal stimulation, or the use of anal dildoes that are moved to the vagina often times lead to fecal contamination and give rise to a very difficult type of vaginitis to diagnose and cure. However, one does not need another partner in order to get fecal contamination during sex play. Using unwashed dildoes or vibrators or sharing them with another person may be the source for introducing unusual bacteria into the vagina. Once the etiology of the infection is determined, treatment by a change of sexual practice may be efficacious.

The second source of fecal contamination can be the patient's dress and sanitary habits. Many women were not taught to wipe the vaginal and rectal area from front to back. Even if they were taught this, they may not do it that way every time, because it may seem unimportant or inconvenient to them. However, if you always wipe from front to back, the perineum may be only blotted or wiped dry with urine and fecal material left smeared on the skin. The amount of secondary bacterial growth that then occurs depends on the frequency of bathing, the temperature and moisture in the area, and the patient's anatomy. Certainly, marked obesity, overhanging labia and/or profuse perineal hair are more likely to be associated with fecal or urine soilage.

Pantyhose, nylon panties, panty girdles, other girdles and crotch-hugging (non-absorbent) jeans all serve to increase the temperature and moisture in the area. Women with recurrent infections should be advised to change their dress habits and sanitary practices so as to decrease microbial residue in the area. Patients should be given instructions to improve their perineal/vaginal hygiene.

SUMMARY

A careful diagnosis should be made by:

(1) obtaining a complete history including use of possible contact irritants, sexual activities, associated illnesses, characteristic appearance, odor, etc. of the lesion;
(2) appropriate diagnostic measures after physical examination include a Pap, wet smear, potassium hydroxide preparation, Gram stain (possible Dif-Quick stain in the presence of extreme leukocytosis with no visible trichomonads), and the use of culture media for recurrent infections;
(3) using an appropriate selection of therapeutic agents, either singly or in combination, for a sufficient period of time to cure a primary lesion;
(4) reassessing and reinforcing compliance with therapy should the lesion persist or recur; and
(5) giving the patient a set of instructions to facilitate therapy of the original infection and prevent future infections.

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71
Infectious complications associated with the intrauterine contraceptive device

The placement of a foreign body within the endometrial cavity for contraception had a partial genesis in Arabic medicine. Dating back to about the 16th century, desert nomads had placed stones in the uterine cavities of camels to prevent conception prior to and during safaris. In the late 1920s and 1930s, a flurry of enthusiasm flourished centering about the Grafenberg ring as a possible mode of contraception, only to disappear in a relatively short period of time due to the infectious complications which ensued. The rekindling of interest in the use of foreign bodies as a mode of contraception was predicated on a technologic innovation, namely, the development of inert flexible plastic with a memory from which intrauterine contraceptive devices (IUDs) could be made.

The insertion of an IUD must be viewed as a relatively non-sterile procedure. But even when superficial erosions are produced, the mere introduction of organisms is insufficient to produce disease. The presence of a healthy viable endometrium with its high oxidation-reduction potential is an effective barrier against all organisms except for the virulent cocci. Immediately following the insertion of an IUD, in a significant number of instances, bacteria can be recovered from the endometrial cavity by transuterine aspiration. When resampled within 24–72 hours, the endometrial cavity is again sterile.

SIGNIFICANCE OF ENDOMETRIAL BACTERIAL CONTAMINATION

Endometrial contamination is a common event following parturition. Seventy to eighty percent of patients can be demonstrated to have moderate or heavy growth of at least one bacterium. The incidence of positive cultures is progressive with time. While only one of every ten endometrial cultures may be positive postpartum, all cultures will be positive after 24 hours and this type of endometrial infection persists for at least five days. Multiple studies have shown no difference between the types of flora in cultures of asymptomatic and clinically infected puerperal uteri. Since the overwhelming number of women are infected during the immediate postpartum period, the obvious question is why do only 1% to 2% of women delivering vaginally and without obstetrical trauma go on to develop disease, more specifically, endometritis? Underlying the necrotic decidua and clotted blood is a layer of healthy endometrial tissue whose oxidation-reduction potential usually precludes the penetration of superficial infection due to Class II and Class III anaerobes. Microaerophilic Class II and Class III anaerobes do not represent a significant cause of postpartum endometritis following spontaneous vaginal delivery.

There is high probability that some contamination of the endometrial cavity occurs at the time of menstruation; however, just as with bacterial contamination associated with

parturition, the endometrium is able to rid itself of this inoculum. The transient contaminations which occur at the time of the menses or with sexual intercourse at selected times in the menstrual cycle appear to be of limited biological significance barring the presence of an exogenous virulent pathogen.

Bacterial contamination of the endometrial cavity can occur at the time of insertion of the intrauterine contraceptive device. In this setting, infection of the endometrium, unless associated with significant

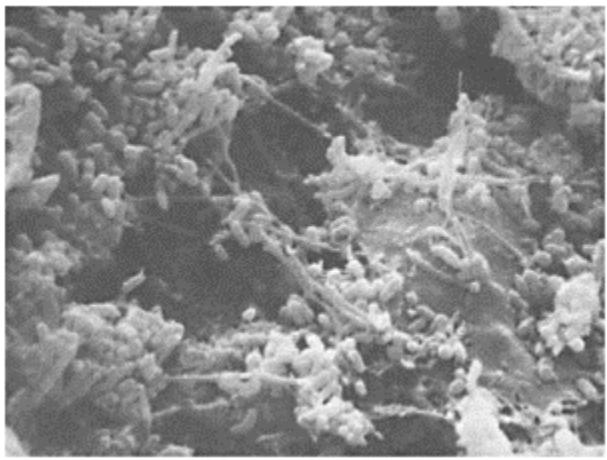

Figure 71.1 Scanning electron microscopic photomicrograph of the surface of an intrauterine contraceptive device which demonstrates bacteria interspersed within calcium-coated matter (×5000)

endometrial penetration, is usually of limited clinical significance, and within a short period of time the infection is cleared. Relative comparable observations have been observed in the baboon model system. Skangalis *et al.* studied a group of 33 female baboons into whose uteri an IUD had been inserted. They observed that bacteria could be present in the uteri of baboons for an extended period of time and function in a 'benign, almost normal flora fashion' without producing disease.

EFFECTS OF THE IUD

The histologic alterations in the endometrium induced by the presence of an IUD include microscopic erosions of the endometrial surface (particularly at the points of contact), a tendency toward focal predecidual changes, an increase in mononuclear cells, and an increase in local vascularity. Areas with such changes can be shown to have increased

glucose and oxygen consumption and presumably an altered oxidation-reduction potential.

With time, the IUD *per se* is biophysiologically altered. These surface alterations may facilitate bacterial adherence and partially facilitate circumvention of host cell phagocytosis. Marrie and Costerton studied 10 IUDs by scanning and transmission electron microscopy. All the devices had material adherent to them. The amount of this material varied considerably. Many different morphologic types of bacteria were observed adhering to the devices, often buried in a thick biofilm. Electron microprobe analysis revealed the presence of calcium in the biofilm formed by bacterial colonization.

Schmidt *et al.* postulated that calcium deposits were apparently vital to the establishment of infection. Calcium is a component of a heterogeneous crust or coating containing both organic and inorganic materials (Figure 71.1). The crust appears on the string of an IUD as well as on its body and provides a cozy niche for actinomyces and other anaerobes where they are safe from the body's normal immune defenses. They demonstrated a variety of bacteria growing both in and under the calcium coating.

The histological alterations associated with the IUD may not be entirely restricted to the endometrium. Smith and Soderstrom have demonstrated a lymphocytic infiltration of the fallopian tube segment in fewer than 1 % of non-IUD users undergoing tubal sterilization, as opposed to a 47% incidence in IUD users. Beerthuizen *et al.* prospectively analyzed the pathomorphological changes in the oviducts in 253 women who underwent voluntary sterilization via posterior colpotomy in order to investigate the effect of the intrauterine device. Some form of histological change was found in 54% of the IUD group and in only 6% of the control group.

Tietze, among others, has documented an increased incidence of ectopic pregnancies in IUD users. This observation focused attention on the hypothesis that these alterations may have, in certain instances, a functional significance in terms of the ovum transport.

MECHANICAL PROBLEMS

Transuterine penetration of the IUD may occur. If both the myometrium and the peritoneal serosal surface are transgressed, depending on the type of device, certain complications can ensue which may ultimately result in infectious morbidity (Table 71.1). Complications due to the linear-shaped inert plastic IUDs have been

Table 71.1 Potential complications secondary to transuterine migration

Copper T or Copper 7	Induction of omental masses
Ring types	Intestinal obstruction
Dalkon Shield	Intestinal perforation and abscess due to peritonitis
Saf-T-Coil or Lippes Loop	Rare uterine perforation
Majzlin Spring	Uterine perforation

relatively few. If an IUD is of a closed configuration, such as a ring, intestinal obstruction can occur when the bowel becomes incarcerated within the enclosed area of the IUD. Copper-containing IUDs, when present in the peritoneal cavity, have been the cause of omental masses. The most significant cause of infectious morbidity is the penetration of a Dalkon Shield into the peritoneal cavity. Unlike the Lippes Loop, the Dalkon Shield, if it becomes entrapped adjacent to the bowel, tends to penetrate into the bowel, causing perforation and subsequent intestinal abscesses or peritonitis.

INFECTIOUS COMPLICATIONS ASSOCIATED WITH THE IUD

The infectious morbidity associated with the IUD can be broken down into four major categories:

(1) infectious morbidity associated with the insertion of the IUD;
(2) the induction of a chronic anaerobic endometritis (CAE);
(3) the superimposition of exogenous sexually transmitted disease (STD); and
(4) the induction of infectious morbidity in the pregnant patient using the IUD.

Insertional infectious morbidity

Infectious morbidity associated with the insertion of the IUD can be broken down into two subcategories:

(1) infectious morbidity secondary to incomplete perforation and the resultant trauma to the endomyometrium; and
(2) the introduction of exogenous pathogens to the female genital tract and the probable provision of an effective portal of entry.

The insertion of an IUD necessitates the taking of a sterile object, the IUD, traversing a contaminated microbiological environment, the endocervix, and introducing it into a sterile environment, namely the endometrial cavity. In the course of insertion, bacteria which reside as constituents of the bacterial flora of the endocervical canal are mechanically introduced into the endometrial cavity. Despite the mechanical disruption of the cutaneous barrier and secondary bleeding, there is no ensuing infectious morbidity unless an exogenous pathogen is present or significant myometrial trauma is induced. The reason that the initial contamination of the endometrial cavity does not produce disease is its oxidation-reduction potential. The majority of the constituents of the biological flora of the female genital tract are by themselves without major pathogenic potential, unless there is a significant alteration in the host defense mechanism which permits their replication and clinical expression. The prime prerequisite for effective anaerobic replication is an alteration in the oxidation-reduction potential. The oxidation-reduction potential of healthy endometrial tissue precludes anything but transient superficial replication of the microaerophilic Class II anaerobes. The normal anaerobic constituents of the female genital tract are usually of little or no biological significance by themselves.

Data emanating from a multi-center case controlled study of the National Institute of Health and Human Development showed that the highest risk of pelvic inflammatory disease (PID) occurred in the first three months following IUD insertion (a relative risk of 1.8 compared with women using no contraception).

A significant proportion of infectious morbidity seen in the immediate postinsertion period is due to the presence of EXOGENOUS organisms. The two bacteria most consistently associated with postinsertional infectious complications are:

(1) The group A beta-hemolytic streptococci; and
(2) *Neisseria gonorrhoeae.*

Group A beta-hemolytic streptococci

Given the initial breach in the mucosal integrity, the group A beta-hemolytic streptococci can produce fulminating infection which, if not quickly checked, can be associated with a lethal outcome. The patient gets sick within the first 24 hours and appears quite toxic. The temperature is markedly elevated (greater than 39ºC). The uterus is exquisitely tender, but there is little discharge other than a sparse, salmon-colored, watery exudate.

Neisseria gonorrhoeae

The bleeding induced by trauma of insertion may be of sufficient magnitude to be the catalytic element for the production of disease due to *Neisseria gonorrhoeae*. The onset of disease tends to be delayed, usually beyond 24 hours. Clinical expression of disease is milder in comparison to that induced by the group A (C or G) beta-hemolytic streptococci. The degree of uterine tenderness is markedly less. A purulent discharge can be readily demonstrated.

Irrespective of which bacteria produces disease, a presumptive diagnosis is readily inferred from the Gram stain analysis. A definitive diagnosis is established by bacteriological culture.

The delayed-onset insertion endometritis appears to be primarily related to myometrial penetration. Insertional trauma creates the opportunity for endogenous organisms to combine and, through the anaerobic progression or a variant thereof, produce disease. If, in the course of the introduction of the IUD, the device is forced through the endometrium and embedded deep into the myometrium, one has effectively circumvented the barrier constituted by the endometrial surface and is contamination by a Class II anaerobe or anaerobes can result. Infectious morbidity due to endogenous organisms may ensue. It is probable that some of the clustering beyond the immediate-onset type of endometritis may be tied to increased probability of contact with a significant STD pathogen. Because there have been no attempts to dissect superimposition of STDs on IUD utilization, the epidemiological studies concerning the causation of disease in the first 90 days postinsertion have been gravely flawed.

CHRONIC ANAEROBIC ENDOMETRITIS

The presence of a foreign body within the endometrial cavity appears to select for bacterial colonization within the endometrial cavity with time; however, the factors selecting for disease are unique from those which select for infection. The perception of chronic anaerobic endometritis (CAE) retrospectively emanated from an extremely astute observation that the Papanicolaou smears of an IUD user who died of disseminated actinomycosis exhibited cytological evidence of the infection with that organism for a period of years.

The presence of bacteria morphologically consistent with actinomyces on Papanicolaou stained smears is a phenomenon seen almost exclusively in women using the IUD as their mode of contraception. When confirmation is attempted with fluorescent isothiocyanatelabeled antisera against *Actinomyces israelii*, approximately 50% exhibit specific immunofluorescence. Part of the explanation is that while *A. israelii* is the most common, *A. naeslundii, A. eriksonii* and *Arachnia proprionica* may be the causative agents. No one specific type of IUD predisposes to actinomyces growth. The single most common factor among IUD users with actinomyces infection is the duration of use. Almost 85% of the cases occur in women who had worn an IUD for three or more years.

Pettit *et al.* carried out a case-control study to determine the factors associated with the presence of actinomyces-like organisms on cervicovaginal Pap smears in users of the IUD. Among about 80000 Papanicolaou smears examined in one year, actinomyces-like organisms were identified on 107 smears; all but three smears were from IUD users. Compared with IUD users who did not have actinomyces-like organisms on Pap smears, those with actinomyces-like organisms had used the IUD for more years. No significant association of actinomyces-like organisms with the type of IUD was found after controlling for differences in duration of use between users of various IUDs. The percentage of women reporting gynecologic symptoms (vaginal discharge, pelvic pain, abnormal bleeding) also did not differ significantly between IUD users with and without actinomyces-like organisms on Pap smear.

Valicenti *et al.* prospectively screened the cervical Pap smears from 69 925 women for the presence of *A. israelii*. The organism was not identified in non-IUD wearers. The prevalence of *A. israelii* among IUD wearers ranged from 1.6% (general population) to 5.3% (clinic population). Prolonged IUD use again appeared to predispose to a higher incidence of infection.

In those patients whose IUDs were removed and not replaced, subsequent Pap smears failed to reveal actinomyces. From this type of data, it has been concluded that in the vast majority of cases the organism causes a superficial infection of the endometrium which can be subsequently shed with the menstrual period. While uterine actinomyces is usually superficial, the organism is potentially invasive. Systemic actinomyces infection, if it develops, may be fatal.

The low incidence of infectious complications seen with the Progestasert IUD has been postulated to be the result of the regular practice of yearly exchange. Keebler *et al.* demonstrated that while first cytological immunological evidence of *A. israelii* was

noticed after seven months, the risk of infection increased significantly when the IUD had been in place for more than two years.

Van Bogaert studied a group of 65 IUD users during a period of 165 years of use (with a mean of 2.6±1.7 years per woman). The main complaint which differed significantly from the 120 controls was the occurrence of spotting in 33.8% of IUD users. Normal endometrial mucosa was found in 36.9% of IUD users and 38.7% of controls. Chronic endometritis was evident in 35.4% of IUD users versus 12.5% of controls; the former were asymptomatic in 25% of the cases. Chronic endometritis occurred 2.2±1.3 years after insertion of the device.

Burkman *et al.* demonstrated that cytological evidence of superinfection with CAE was more frequent in women who had used a single IUD for many years than in cytological preparations obtained from short-term users. The possibility that the tail itself was the mediating factor was suggested by Sparks *et al.* They bacteriologically sampled 22 women undergoing hysterectomy using a multiple biopsy technique. All five uteri with tailless IUDs were sterile, but 15 out of 17 tailed devices contained bacteria. Most isolates were constituents of the normal vaginal flora.

Stadel and Schlesselman from the Contraceptive Evaluation Branch of the National Institute of Health and Human Development had identified in the data from Women's Health Study the fact that continuous use of the same IUD for five or more years appears to increase the risk of PID, requiring extensive surgery, to a greater extent than use for less than five years.

The presence of *A. israelii* in the female genital tract flora is not a critical determinant of disease. Grice and Hafiz cultured the endocervices of IUD users and non-IUD users. Of 78 users of IUDs, 20 (25.6%) were culture positive. Of the 63 women using various other forms of contraception, 12 (19%) were culture positive. None of these 12 women had an IUD or foreign body *in situ*. Their data were consistent with the contention that *Actinomyces* species may be a part of the commensal flora of the female genital tract.

Using immunofluoresence, Curtis and Pine demonstrated either *A. israelii, A. naeslundii* or *Arachnia propionica* in cervicovaginal mucus from 36% of 50 women. One or more of these organisms was found in a surprising 27% of those with neither IUD nor intravaginal foreign bodies. Among those women who harbored actinomyces, the average duration of continuous IUD use was 5.3 years; the comparable figure for those with no infection was 2.1 years.

Most patients who develop unilateral tubo-ovarian complexes have *A. israelii* as a part of a polymicrobial chronic infection of the endometrial cavity. *A. israelii,* when present, enhances the pathogenic potential of the CAE.

What is now understood is that with the use of the IUD, infection of the endometrial cavity is a common phenomenon. The cumulative pattern, with time, strongly infers that some alteration of the microbiological environment must occur. By changing the biophysical characteristics of the IUD, the endometrium permits bacterial persistence within the endometrial cavity. This infection is able to be present for a prolonged period of time before producing symptomatology and disease. While the majority of patients who developed cytological evidence of actinomyces-like bacteria do not go on to develop disease, a few may develop serious disease. Clinicians have long recognized that after a period of utilization, IUD wearers begin to get into trouble clinically and develop primarily menstrual irregularities or pain on intercourse. Burnhill was among the first to

describe a specific syndrome which tied chronic infection of the endometrium to selected clinical manifestations (Burnhill's Syndrome).

One characteristic pattern of disease associated with CAE is the 'unilateral tubo-ovarian complex'. The unilateral tubo-ovarian complex is a histological and not a clinical diagnosis. What is required is the ability to look at both fallopian tubes and demonstrate clear presence of disease in one fallopian tube and minimal or no disease present in the contralateral tube. This is different from unilateral tubo-ovarian complex seen with the traditional STDs such as gonorrhea or chlamydia. In these clinical settings, the bilateralness of the disease, while not clinically overt, is microscopically documentable. Why does unilateral local salpingitis occur? It has been postulated that with time the contact points of the IUD cause pressure necrosis and ultimate penetration of the basialis layer. Once infection extends into the myometrium, it has effectively circumvented a major host defense mechanism which had previously precluded constituents of vaginal flora which produced the chronic infection of the endometrial cavity from attaining significant potentially life-threatening proportions.

Clinical recognition of disease takes various forms. The majority of women have little in the way of symptomatology other than minor irregularities with the menstrual period which occur after a prolonged period of normal menses. In its asymptomatic form, CAE is diagnosed by the appearance of Gram-positive *A. israelli* (Gupta lesions) present in the Pap smear. Progression of disease may result in menstrual irregularities, foul-smelling intermenstrual discharge, and/or dyspareunia, either singularly or in combination. The full-blown clustering of signs and symptoms is known as Burnhill's syndrome. The incidence of infection/disease appears to be partially governed by the endocervical flora. Women with chronic cervicitis appear to develop IUD-associated CAE more readily than women whose initial bacterial flora harbored the aerobic lactobacilli. Although their documentation is not well recorded in the literature, a number of *forme fruste* of Burnhill's syndrome probably exists. There are a significant number of women with IUDs as their mode of contraception, who present their gynecologists with complaints of 'difficult periods', characterized by excessive cramping and more profuse bleeding. They are treated with a short course of a new generation tetracycline or semisynthetic penicillin and their symptoms abate for a period of time. The response to a therapeutic challenge suggests that many of these patients have CAE.

Management of IUD in patients with CAE

Once a patient with an IUD develops CAE, how should she be managed? If the patient is asymptomatic and the pelvic examination and cytological smear are unremarkable, the IUD can probably be pulled out without antimicrobial coverage.

When the patient has cytological evidence of CAE and meets one of the following criteria:

(1) IUD use is less than five consecutive months;
(2) the IUD is in place more than three years but there is no evidence of Burnhill's Syndrome;
(3) elevated erythrocyte sedimentation rate; or
(4) mass is evident,

it is advocated that a patient be placed on antibiotic therapy at least one hour prior to the device removal and that the drug be continued for two to three days. The drug of choice is either doxycycline or amoxicillin. Metronidazole would be an excellent drug, were it not for its relative ineffectiveness against *A. israelii*. If systemic symptoms referable to the female genital tract or Burnhill's syndrome, an elevated erythrocyte sedimentation rate and abnormal pelvic examination are present, the patient should be evaluated for the possible presence of a tubo-ovarian complex and managed appropriately.

Chatwanani and Amin-Hanjani reported on 173 patients with IUD-associated actinomyces-like organisms detected on Pap smears. The patients were managed by IUD removal with or without antibiotic therapy, antibiotic therapy alone, or no treatment at all. Results were that the success rate as reflected in negative follow-up smear was 100% for IUD removal combined with antibiotics, 97.4% for IUD removal alone, and 36.8% for antibiotics therapy alone.

If a patient with CAE desires to continue that mode of contraception and IUDs are available, what can be done is to remove the IUD under antibiotic coverage, allow two menstrual periods to ensue, and reinsert. It is appropriate to inform the patient as to the signs and symptoms of CAE as well as the potential risks to herself. An appropriate informed consent which documents the fact that the physician has been an agent of the patient and has fulfilled his/her duty as counselor and advocate must be clearly documented in the chart. Monitoring with cytological smears at least every two months until three sets of postinsertional cytological smears are negative for the presence of Gupta bodies is advocated. Thereafter, cytological monitoring can be done on a bi-yearly basis. If cytological evidence of infection reappears, it is strongly recommended that an alternate mode of contraception be implemented.

Unilateral tubo-ovarian abscess is considered to be the ultimate consequence of IUD-induced CAE. If due to CAE, the induction of tubo-ovarian disease requires transgressions of the endometrium by the IUD in close proximity to the orifice of the fallopian tube, particularly when *Actinomyces israelii* or *Actinomyces* species are constituents of this polymicrobial anaerobic infection. With a true unilateral tubo-ovarian abscess, there is no evidence of significant disease in the contralateral tube.

The majority of patients present with a prodrome consisting of vague abdominal pains and dyspareunia. Most of these patients have prior symptomatology consistent with Burnhill's syndrome or a *forme fruste*. When indicated, surgical intervention should be as conservative as possible.

The management of a unilateral tubo-ovarian abscess is not well defined. The two primary therapeutic options are:

(1) the utilization of conservative surgery; and
(2) the commitment to long-term medical therapy and careful monitoring with the intent of allowing the patient the opportunity to conceive without surgical intervention on the contralateral tube.

For the latter approach to be adopted, the patient must have an excellent biological response to antimicrobial therapy. The criteria used to judge whether or not the patient achieves an excellent clinical response are:

(1) resolution of fever under antibiotic therapy;
(2) loss of mass tenderness; and

(3) return to normal of the white blood cell count, erythrocyte sedimentation rate, and the C-reactive protein.

While initial reduction in size of the tubo-ovarian abscess is not mandatory, the mass should be followed by serial ultrasonographic measurements. Should the mass remain tender, stable in size and the leukocytosis persists, despite adequate and prolonged antibiotic therapy, conservative surgical intervention is probably indicated. If aspiration of the complex is not therapeutic or if there is reactivation of tubal disease at a subsequent point in time following medical management, surgery is often indicated.

For a program of medical management to be implemented, the patient must be willing to accept an incremental increased personal risk: the goal being the preservation to the maximum degree of future fertility. The duration of antimicrobial therapy in these patients is not well established and should be individualized in each case. As a rule of thumb, presuming all other clinical criteria have been met, treatment should be extended until the return of the erythrocyte sedimentation rate to normal.

SURGICAL COMPLICATIONS IN ASSOCIATION WITH IUD-INDUCED ANAEROBIC ENDOMETRITIS

Chronic anaerobic endometritis induced by an IUD may be the cause of serious infectious morbidity in a number of situations.

The presence of CAE with menstrual irregularities and more difficult periods may precipitate the patient's request for a tubal ligation. If the IUD is removed at the time of surgery, subsequent development of a tubal abscess is a not uncommon complication. The presence of chronic anaerobic infection coupled with that of devitalization of tissue and secondary microhematoma formation create ideal conditions for the immediate anaerobic syndrome to ensue. If the patient is suspected of having a *forme fruste* of Burnhill's syndrome, remove the IUD under appropriate antibiotic coverage at some time interval before or after surgery.

ENHANCED CLINICAL EXPRESSION OF OTHER SEXUALLY TRANSMITTED DISEASES

The IUD causes a leukocytic outpouring in response to the presence of a foreign body in the endometrial cavity. The inflammatory response induced alters the local pH. The rise in pH is hypothesized to potentiate replication of selected venereally-acquired exogenous pathogens. The clinical expression of infection due to *Neisseria gonorrhoeae* is governed, in part, by alterations in pH. The IUD does not increase the incidence of gonococcal infection but it may influence the incidence of gonococcal disease. The incidence of acute salpingitis, Stage I and II, is threefold greater in IUD users than non-IUD users.

Twenty-five reports have found a significantly increased risk of PID or tubal infertility among IUD users. These 25 studies, conducted in many different countries by different investigators with different diagnostic criteria, have all found an increased risk of PID or its sequelae among IUD users, which argues strongly for a causal relationship. The

strength of this association in the most objective studies ranges from a relative risk of 1.5 to 2.6.

Results from analysis of the Women's Health Study data found that women who were currently using an IUD had a relative risk of PID of 1.9 (95% confidence limits 1.5 to 2.4) compared with women who were using no method of contraception at the time of their hospitalization. However, approximately 20% of this increase in relative risk could be accounted for by the marked increase in risk associated with use of the Dalkon Shield. Women using the Dalkon Shield had more than eight-fold increase in risk of PID, whereas women using other IUD types had a risk of 1.6 (1.2–2.0) compared with women using no method of contraception. The increase in risk associated with Dalkon Shield use did not appear to be explained by confounding effects or by biases such as hospitalization or recall. The Women's Health Study indicated that the Dalkon Shield IUD was different from other IUD types; however, the study provided no indication that other IUD types differed from each other in their risks of PID.

When the impact of women's sexual behavior on the IUD-PID relationship was reanalyzed by the Centers for Disease Control, marital status was demonstrated to be an important variable on the relative risk of PID associated with IUD use. Women reporting only one recent sexual partner, married or cohabiting women had little increase in risk associated with IUD use, whereas previously or never-married IUD users had at least twice the PID risk as women with similar marital status who used no contraception. Lee *et al.* concluded that women who were in mutually monogamous sexual relationships, and therefore at low risk for acquiring an STD, probably had little increase in PID risk from IUD use. However, even in this low risk subgroup of women, PID risk was elevated shortly after IUD insertion, suggesting that the risk associated with IUD use was not entirely related to risk of STD acquisition.

IUDS AND INFERTILITY

Studies published in the late 1970s and 1980s, demonstrated a significant risk of 'PID' among IUD users versus non-users. Unfortunately many of the studies were poorly designed to control for the unmeasured confounding effect of exposure to STDs and in particular *Chlamydia trachomatis*. When reanalysis was done using better comparison groups and separating results according to the type of IUD, Buchan *et al.* could not demonstrate increased risk of PID with medicated devices. Data reported by the World Health Organization by Farley *et al.* and Walsh *et al.* have cited figures for the incidence of PID among IUD users which are comparable to those cited for the general population. Risk of PID appears to be related to insertion, endometrial penetration and exposure to STDs. One of the unfortunate consequences of PID is secondary infertility.

Patients using IUDs have a higher prevalence of inflammatory residues than do non-users. They also have a higher prevalence of chlamydial antibodies. If one examines residue frequency in user versus non-user groups at the same chlamydial antibody level, no difference exists. This is also true if patients with known causes for residues (explained) are excluded and the remainder (unexplained or silent) are grouped according to antibody titer. Guderian and Trobough studied the causal relationship between PID and tubal infertility patients (176 patients had not used an IUD and 69 had used one).

Chlamydial antibody titers were performed on all patients. Although users had a higher overall prevalence of inflammatory residues than non-users, there was no difference in residue prevalence for either group at the same titer levels. No specific type of device appeared to be associated with either an increased or decreased residue frequency. 'Silent' chlamydial infections occurred with equal frequency in both users and non-users.

Gump *et al.* studied 204 infertile women for the possible role of *C. trachomatis* and IUD use as factors related to their infertility. A highly statistically significant correlation ($p<0.001$) was obvious between evidence of prior 'PID' as documented by hysterosalpingograms and/or laparoscopy and the prevalence of chlamydial antibody. A significant correlation ($p=0.01$) could be shown between the prevalence of the antibodies and adnexal adhesions. IUD use could also be shown to correlate significantly with 'PID'. Only about one third of the patients with 'PID' could ever recall having had an illness consistent with 'PID'.

Recently, Hubacher *et al.* reported a large case control study of 1895 women in order to assess the risk of infertility associated with the use of a copper IUD. They concluded that the previous use of a copper IUD is not associated with an increased risk of tubal occlusion among nulligravid women, whereas infection with *C. trachomatis* is.

To date, a definitive study has yet to be done. What is apparent is that the risk of inflammatory complication leading to secondary infertility is relate to exposure to pathogens, insertional trauma or prolonged utilization.

IUD AND PREGNANCY

When an unplanned pregnancy occurs in an IUD wearer, three problems potentially may develop:

(1) ectopic pregnancy;
(2) fetal wastage; and
(3) septic abortion/matemal septicemia.

Ectopic pregnancy

A number of investigators have shown that accidental pregnancies occurring in long-term users of an IUD are more likely to be ectopic than those occurring in short-term users. Data reported from the Oxford Family Planning Association contraceptive study show that 6% (17 of 258) of accidental pregnancies occurring in parous women using an IUD were ectopic, while the corresponding figure for those using other methods of contraception was only 0.5% (3 of 632). There is a positive association between the likelihood of an accidental pregnancy being ectopic and the duration of an IUD. Among the pregnancies occurring up to 24 months after insertion of a device, 2.0% (2 of 101) were extrauterine while the corresponding figure for those pregnancies occurring 49 months or more after insertion was 12.9% (11 of 86). Vessey *et al.*, using the same Oxford Family Planning Association study, have demonstrated that the absolute risk of ectopic pregnancies was found to remain constant with duration of use at approximately 1.2 per 1000 women per year. A woman who presents with a contraceptive failure after

more than three years using an IUD has about a 1 in 10 chance of having an ectopic gestation.

Studies done in the United States by Ory and Edelman have concluded that IUD use was more common in women with ectopic pregnancy than in healthy reproductive-aged women. Approximately 20% of pregnancies occurring in women using IUDs are ectopic. Some of this morbidity is due to concomitant chlamydial infection. Guderian and Trobough demonstrated a 22.5-fold increase in ectopic pregnancy frequency in IUD users with a titer of >1:512 when compared to their non-user group. Women who become pregnant while using an IUD should be carefully counseled as to the risk and signs and symptoms of an ectopic pregnancy.

FETAL WASTAGE

Unplanned pregnancies in women using an IUD are about three time more likely to end in miscarriage than pregnancies occurring under other circumstances. Vessel *et al.* reported that 52% of unplanned pregnancies that occurred among IUD wearers ended in miscarriage, as compared with 17% among women using other methods of birth control at the time of conception. Tatum *et al.* demonstrated that when the device (Copper T IUD) was removed or expelled shortly after conception, the incidence of spontaneous fetal loss was 20.3%, a figure similar to the normal incidence of spontaneous abortion in the study population.

Biologically, the most significant problem is second trimester fetal loss. In contrast to first trimester fetal loss, the projected risk of second trimester fetal loss among women beginning the second trimester of pregnancy without an IUD in place is estimated to be 2%. If the IUD was in place at conception, but was removed during the first trimester of pregnancy, the risk of second trimester fetal loss was increased tenfold. This increase in risk was much greater for septic second trimester fetal loss than for non-septic fetal loss.

Septic abortion/maternal septicemia and death

From 1965 to 1982, more than eight million IUDs have been distributed in the United States. Of the maternal deaths recorded prior to 1977 attributed to IUDs, 16 were attributed to use of the Dalkon Shield, 18 to the Lippes Loop, four to the Saf-T-Coil, two to the Majzlin spring and one to the Bimberg Bow. In two cases, the IUD was not identified.

Analysis of all maternal deaths from spontaneous abortions reported in the period 1972–1974 demonstrated that women dying from spontaneous abortions with an IUD in place were more likely to be young, white, and married than those not wearing a device. The risk of death from spontaneous abortion was 50 times greater for women who continued their pregnancy with a device in place than for those who did not. As compared to other devices, the Dalkon Shield carried an added risk of death.

If septic abortion occurs, the importance of complete evacuation of the uterus cannot be over-stressed. Hurst reported a case of septic shock and disseminated intravascular coagulopathy in a gravida with an IUD. The patient did not respond to appropriate antibiotic therapy. She improved somewhat following uterine curettage; however, the

coagulation abnormalities and evidence of febrile morbidity persisted. Complete resolution did not occur until repeat uterine curettage removed a small amount of residual tissue from the maternal implantation site.

Maternal septicemia and abortion can occur with any of the IUD. The FDA Drug and Device Obstetrical and Gynecological Advisory Committee recommends that patients with an IUD in place who miss their normal menstrual period or who become pregnant seek medical advice as soon as possible for removal of the IUD. Whenever pregnancy coexists with an IUD, irrespective of type, removal is recommended.

THE DALKON SHIELD

The disproportionately large number of cases of septic spontaneous abortions and maternal deaths in women using the Dalkon Shield raised the question of a possible causal relationship between these two events (Figure 71.2). Tatum *et al.* have demonstrated that in lieu of a single or double strand of plastic monofilament, the tail of the Dalkon Shield consists of a bundle of monofilaments enclosed within a thin plastic sheath (Figure 71.3). The standard shield contains approximately 400 separate fibers, whereas the tail of the small shield contains approximately 200 fibers. Bacteria enter the spaces between the fibers within the sheath and are, either by their inherent motility or by capillary action,

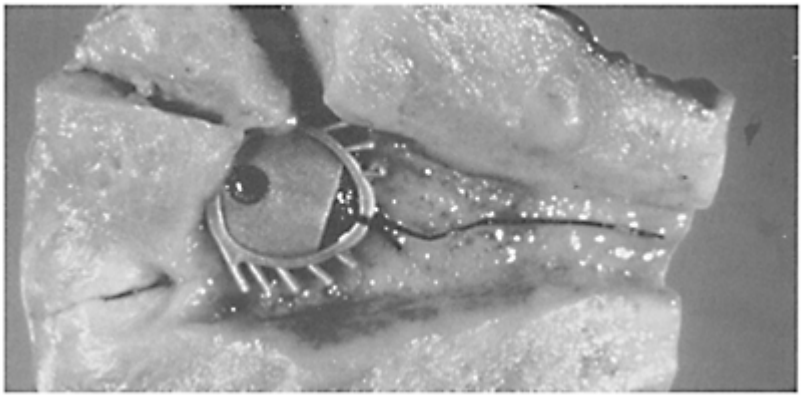

Figure 71.2 Cut section of a uterus containing a Dalkon Shield

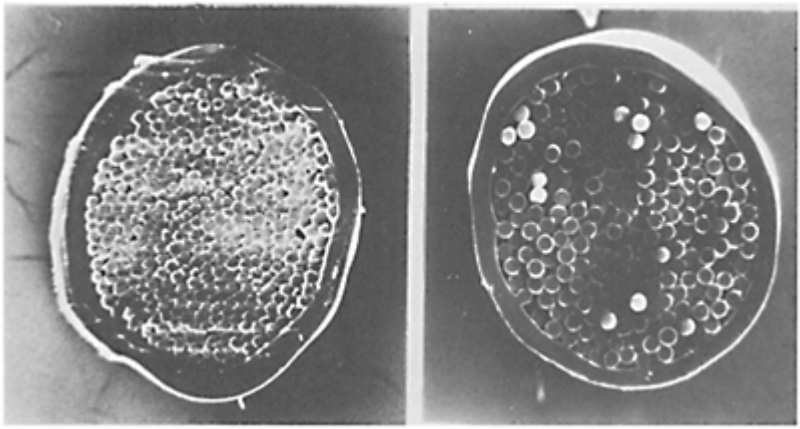

Figure 71.3 Dalkon shield tails, which are composed of 200–400 monofilaments enclosed in a protective sheath (Tatum HJ *et al. J Am Med Assoc* 1975; 231:711)

able to migrate up along the tail (Figure 71.4). The tail functions as a wick for the passage of fluid and bacteria throughout its length all the way to the final double knot at the base of the shield but not through it.

The tails of all major devices, by virtue of their intimate contact with the posterior vaginal pool, are contaminated by the vaginal flora. With pregnancy and progressive uterine enlargement, the tail is drawn up through the mucous plug. The latter is normally a lethal barrier to the viruses, fungi, protozoans, mycoplasmas, bacteria, etc. of the vaginal flora. A monofilament or a double-stranded tail is literally wiped clean. The nylon sheath effectively circumvents this protective mechanism. While septic abortion due to a Lippes Loop characteristically occurs in the latter first trimester, that observed with the Dalkon Shield is a second- to early third-trimester event. While the bacteria attain ingress through the tail, the double knot mechanically blocks

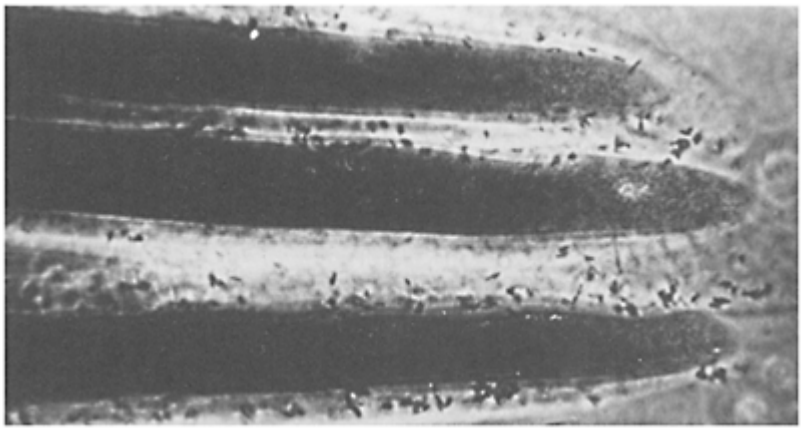

Figure 71.4 Demonstration of bacteria between the individual monofilaments of the Dalkon shield tail (Tatum HJ *et al. J Am Med Assoc* 1975; 231:711)

further migration, and consequently the bacteria must egress by the initial portal of invasion. This accounts for the delayed onset of infectious morbidity and mortality.

When pregnancy occurs in women with an IUD in place, the device should be removed if that can be done without compromising the fetus (Table 71.2). The presence of the IUD string at the os or present in the lower uterine segment usually determines whether or not the IUD will be pulled. There is no question that one runs the theoretic risk of mechanically compromising an established pregnancy; however, maternal considerations and well-being take precedence over those of the fetus. One will do well to counsel the patient that 10% of all pregnancies terminate in abortion. Should abortion then occur, the chances are overwhelming that it is due to a naturally occurring phenomenon and not due to the procedure to which the patient has consented. Such counseling is not only correct in its content, but will go a long way to averting undue guilt on the part of the patient. If the IUD in question is a Dalkon Shield, the course of action should be appropriately aggressive.

THE IUD AND BACTERIAL ENDOCARDITIS

The patient with congenital valvular disease or a prosthesis in certain instances may be at a high-risk for ensuing bacterial endocarditis if the IUD is chosen as the mode of contraception. The insertion of an IUD should be done under antibiotic coverage in a manner similar to that for any surgical procedure. Once the IUD is in place, the patient must be monitored for evidence of intervening anaerobic infection. The best clues are the subsequent development of an intermenstrual, foul-smelling leukorrhea or the appearance of pseudomycelial forms (Gupta lesions) on the Pap smear. Should either develop, it is

our policy to advocate removal of the device under antibiotic coverage (specifically, with ampicillin and gentamicin rather than penicillin and streptomycin).

SUMMARY

Much of the infectious morbidity associated with IUD usage can be averted by:

(1) careful patient selection;
(2) pre-screening high-risk gravidas for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* prior to insertion;
(3) pre-screening for group A streptococci when disease is in high prevalence in the pediatric population;

Table 71.2 Recommendations for the management of the IUD in pregnancy

Condition	***Recommendotions***
First trimester:	
No history of CAB—String at os	Obtain informed consent delineating risk-benefit ratio. Remove.
First trimester:	
One or more synptoms suggestive of CAE. String at os	Obtained informed consent. Then, treatment with an antibiotic with good anaerobic coverage for at least 36 hours prior to IUD removal. (Tetracyclines contraindicated)
First trimester: No string at os	Do not intervene. Instruct patient as to the early signs of infection. Evaluate by ultrasonography as to position with respect to gestational sac. If the string is balled up in lower uterine segment and can be brought down easily, removal possible but not without some risk.

(4) careful insertion of the IUD;
(5) patient education as to the signs of CAE

   (a) intramenstrual spotting or *de novo* menstrual irregularities,
   (b) intramenstrual discharge;

(6) requiring periodic pelvic examination with cytological evaluation;
(7) limiting use of IUD to 24–36 months; and
(8) removing the IUD in all patients with any significant STD involving the female genital tract.

Women who use the IUD must be carefully counseled as to the fact that they are at augmented risk for the development of CAE and its potential complications as well as being at possible augmented risk for spontaneous first trimester abortions, ectopic pregnancies and septic abortions should this mode of contraception fail. Should they come in contact with selected STD organisms, the probability of overt destructive disease is enhanced. Women continuing to use the IUD need to be educated as to the early signs

and symptoms of clinically significant CAE. Continued use of the IUD should be coupled with a commitment to at least annual cytological and medical re-evaluation. If the problems of CAE are to be circumvented, it is best that women change their form of IUD within a two- but not later than three-year period. If a Dalkon Shield is still the mode of contraception, its removal is strongly urged.

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72
Toxic shock syndrome

Prior to 1979, toxic shock syndrome (TSS) was a rare disease described primarily in children. During the 1979–1981 epidemic, TSS became recognized as a disease that occurs primarily in menstruating women using tampons. Tampon users were demonstrated to be 18 times more likely to develop menstrual TSS as nonusers. While recent focus has shifted to non-menstrual cases which have occurred in conjunction with wound infections, postpartum endometritis and vaginitis, the predominance of cases continues to be related to menstruation.

PATHOGENESIS

Staphylococcus aureus can be recovered from the posterior vaginal pool/endocervix in 97% of the cases of TSS.

The demographic appearance of numerically significant cases of TSS coincided with the introduction of superabsorbent tampons. The dramatic nature of the presenting symptoms of the illness in otherwise healthy women and its recent incidence largely preclude previous lack of recognition.

The pathogenic mechanism for the association of tampons with TSS has not been adequately explained. Berkley *et al.* showed that all users of all brands of tampons have an elevated risk when compared to nonusers. Regardless of the composition of the tampon, absorbency increased the odds ratio for TSS. The chemical composition of the tampons also influenced the odds ratio. Polyacrylate-containing tampons had odds ratios which were elevated. Certain materials are superior to unaltered cotton in providing a more absorbent fiber. Nutrients are efficiently drawn in, concentrating protein between fibers, and thereby creating an ideal physiochemical environment for the amplification of TSS-toxin 1 (TSST-1) and other toxins. The greatest stimulation of TSST-1 was observed with, in decreasing order: polyester and carboxymethyl cellulose, polyacrylates, viscose rayon, gelatin foam, polyurethane, and cotton. The use of a low-absorbency tampon appears to reduce the risk of TSS in tampon users (Figure 72.1).

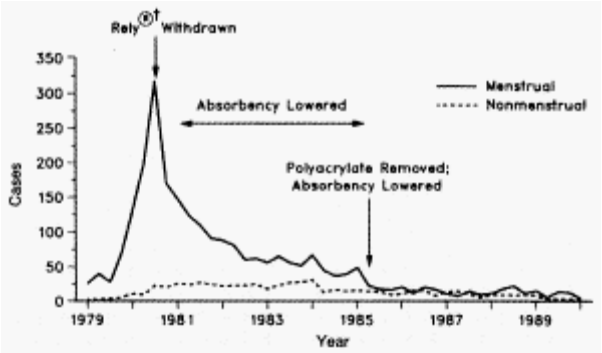

Figure 72.1 Reported cases of toxic-shock syndrome,* by quarter—United States, 1980–1990

*Includes only cases meeting the CDC case definition.

†Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services. (*MMWR* 1990; Vol 39/No 25)

TSS specific toxins

TSS-toxin 1 is a protein with a molecular weight of approximately 24 000 daltons and has been proposed as the toxin responsible for TSS. TSST-1 production has been demonstrated in 90–100% of *Staphylococcus aureus* strains recovered from women with menstrual TSS. Investigators have been able to induce TSS-like illness in 60% of rabbits injected subcutaneously with TSST-1 negative isolates of *S. aureus*. These results suggested that other as yet unrecognized toxins play a role in TSS and that TSST-1 may not be totally responsible for the pathogenesis of toxic shock. Musser *et al.* analyzed the genetic relationships among 315 isolates of the bacterium *S. aureus* expressing TSST-1 recovered primarily from humans with TSS in five countries on two continents. A single clone (ET 41) accounted for 88% of cases of TSS with a female urogenital focus and 53% of TSS cases involving non-urogenital (predominantly wound) infections. With few exceptions, strains representing different phylogenetic lines had a characteristic TSST-1 gene restriction fragment.

The recovery of a single clone from the majority of individuals afflicted with TSS having a urogenital focus and from the genital tract of a large proportion of asymptomatic female carriers strongly suggests that this clone is especially well adapted for colonization of these anatomic sites.

Non-enteric toxins

The ability of extracellular culture filtrates of *S. aureus* to cause inflammatory reactions after inoculation into experimental animals was first reported in 1885. It has subsequently been shown that selected strains of *S. aureus* are capable of elaborating an impressive spectrum of non-enteric toxins. These toxins include exfoliative toxins A and B, alpha, beta, delta, and gamma toxins, and leukocidins. The exfoliative toxins (A and B) are a mixture of two or more products capable of producing intraepidermal cleavage. They are distinct from the other non-enteric toxins. Exfoliative toxin production is not limited to a specific phage group strain of *S. aureus*. The basic mechanism by which the alpha toxin works is membrane damage. While the beta, delta, and gamma toxins all exert profound effects on cell membranes, the importance of alpha toxin is due to its qualitative as well as quantitative effect. Alpha toxin has always been considered to play a significant role in the pathogenesis of staphylococcal disease. The alpha toxin is hemolytic to erythrocytes and cytotoxic and cytolytic to a wide variety of cells. In experimental animal model systems, the principal sites of cytotoxicity are the kidney, where the toxin produces renal necrosis, and the intravascular compartment, where it produces a consumptive coagulopathy. If present in sufficient quantities, alpha toxin causes constriction of the coronary arteries, decreased cardiac output, and ultimately systolic arrest. Beta toxin produces membrane damage via enzymatic activity (sphingomyelinase) and significant degradation of membrane sphingomyelin with secondary effects on membrane permeability.

The ability of the beta toxin to damage cell membrane is directly related to its sphingomyelin content; hence, its effects tend to be more specific than those of the alpha toxin. The delta toxin differs from the other membrane-damaging bacterial toxins elaborated by *S. aureus* by its relatively hydrophobic nature and low degree of cellular specificity. The delta toxin behaves similarly to cholera toxin. In high doses, it causes histologic damage to the ileum and blocks water absorption. In low doses, it causes significant changes in intestinal iron transport even before cyclic adenosine 3′5′ monophosphate levels increase. The gamma toxins have been described only recently. The data concerning specificity of site of cell membrane damage are limited. The clinical manifestation of TSS appears to be the result of the cumulative effect of non-enteric toxin production (Table 72.1).

Not every strain of *S. aureus* can produce exfoliative toxins. Approximately 14% of randomly gathered strains of *S. aureus* can produce the complete spectrum of toxins (exfoliative toxins A and B, alpha, beta, delta, and gamma toxins) incriminated in the pathogenesis of TSS.

The intrigue of TSS is not necessarily why it occurs, but rather why it doesn't occur more frequently. The Centers for Disease Control (CDC) have estimated that 10% of women harbor *S. aureus* as a constituent of the vaginal flora. Since superabsorbent tampons account for 70% of the tampons sold, the recorded incidence of TSS precludes a one-to-one correlation between the presence of *S. aureus* as a constituent of the bacterial flora of the female genital tract and the use of superabsorbent tampons. These facts suggest that other variables select for disease. Not every strain of *S. aureus* elaborates either exfoliative toxin A or B. Even when the lack of genetic capability of the majority of *S. aureus* strains to produce toxin is taken into account, the resultant numbers merely suggest that the genetic endowment of a given strain of *S. aureus* selects for the potential

for disease rather than for the actual disease. The critical event selecting for disease, given a potential TSS strain of *S. aureus,* is the quantitative increase in toxins produced

Table 72.1 Proposed pathogenesis of toxic shock syndrome (TSS): a cumulative effect of non-enteric bacterial toxin production by selected strains of *Staphylococcus aureus*

Clinical evidence of TSS	***Proposed mechanism of action***	***Implicated non-enteric toxin of S.aureus***
Fever	Secondary to exogenous pyrogens produced by *S. aureus* and endogenous pyrogens released from damaged hematopoietic and endothelial cells	Alpha, beta, delta, and gamma toxins
Rash: diffuse, macular erythroderma and hyperemia of mucous membranes	Secondary to membrane damage involving endothelium and smooth muscle	Alpha, beta and delta toxins
Desquamation of palms and soles	Secondary to intraepithelial cleavage	Exfoliative A and B
Diarrhea	Secondary to inhibition of water absorption from small bowel	Delta toxin
Rising BUN or creatinine (at least twice upper limits of normal)	Secondary to select renal damage	Alpha toxin
Biochemical SGOT/SGPT evidence of hepatocellular dysfunction and central nervous system dysfunction/headache	Combination of secondary vascular and membrane damage	Alpha, beta, delta, and gamma toxins
Hypotension	Secondary to smooth muscle effect and cell membrane damage	Alpha, beta, delta, and gamma toxins

BUN, blood urea nitrogen; SGOT, serum aspartate aminotransferase; SGPT, serum alanine aminotransferase

and secondary to the increased availability of an appropriate growth substrate.

TSS AND CONTRACEPTIVES

Different modes of contraception can also influence the probability of TSS.

Oral contraceptives

Preliminary data have suggested that the use of oral contraceptives is a protective factor against TSS. The mechanism by which this is achieved is hypothesized to be the

reduction in menstrual blood loss which occurs in users of combined oral contraceptives. This phenomenon may have introduced bias into the prior case control studies between TSS and tampon use. Women who take oral contraceptives probably require less absorption and menstrual protection because of lighter menstrual blood loss.

Vaginal contraceptive sponge

Faich *et al.* described 13 cases of TSS which were thought to be connected with the use of the contraceptive sponge. Three cases evolved during the puerperium or menstrual period. One case occurred in a woman who kept the sponge in place for more than 30 hours. Four cases involved difficulty in removing the sponge which resulted in its fragmentation. Nine of the 13 cases related to sponge use were not associated with predisposing factors. Using estimates of background of nonmenstrual TSS, these investigators have conjectured that the rate of TSS in sponge users might be elevated above the estimated background but that the risk of this complication is very low. Traumatic manipulation of the sponge, use during menstruation or the puerperium, and prolonged retention of the sponge may increase the risk of occurrence. The CDC had argued that, despite these superficial similarities to the situation which existed with respect to tampons in the 1980s, withdrawal of the vaginal contraceptive sponge from the market is not warranted by the data to date. What is important is to eliminate those cases which should have never been. Postpartum women and women who have had menstrual TSS previously should avoid using the contraceptive sponge. The sponge should not be used during menstruation and should not be left in place more than 30 hours. Women who choose to use the sponge should read the package insertion carefully and be aware of the signs and symptoms of TSS.

Table 72.2 Case definition of toxic shock syndrome

Fever: temperature 38.9ºC

Rash: diffuse macular erythroderma

Desquamation of palms and soles one to two weeks after onset of illness

Hypotension: systolic blood pressure≤90 mmHg for adults, below fifth percentile by age for children below 16 years of age, orthostatic drop in diastolic blood pressure≥15 mmHg from lying to sitting, or orthostatic syncope

Multisystem involvement—three or more of the following:

Gastrointestinal: vomiting or diarrhea at onset of illness

Muscular: severe myalgia or creatinine phosphokinase level at least twice the upper limit of normal for laboratory

Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia

Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (≥5 white cells per high-power field) in the absence of urinary tract infection

Hepatic: total bilirubin, SGOT, or SGPT at least twice the upper limit of normal for laboratory

Hematologic: platelets≤100000 per cubic millimeter

Central nervous system: disorientation or alterations in consciousness without focal neurologic sign when fever and hypotension are absent

Negative results on the following tests, if obtained:
Blood, throat (Group A beta-hemolytic streptococci), or cerebrospinal fluid cultures
Rise in titer to Rocky Mountain spotted fever, leptospirosis, or measles

SGOT, serum aspartate aminotransferase; SGPT, serum alanine aminotransferase (*MMWR* 1980; 29:441)

Contraceptive diaphragm

A number of cases have been reported of TSS developing in non-menstruating diaphragm users. In all but one case, the development of TSS was associated with prolonged retention of the diaphragm for 36 hours or more. In the cases described, in addition to the mucosal hyperemia, a significant purulent discharge characterized as being yellowish-green and sometimes foul-smelling was noted. Although a rare occurrence, recognition that TSS can occur in women using barrier contraception is important so that early diagnosis can be implemented. The prolonged use of a diaphragm is to be avoided, particularly in women who have previously manifested TSS. The appearance of a vaginal discharge occurring in a woman who uses a diaphragm may be sufficient grounds for discontinuation of its use. The rarity of TSS in users of vaginal barrier contraception may be related to the concomitant use of antibacterial spermicides. The use of spermicides retards bacterial growth and may increase the length of time a device can be retained before bacterial replication and toxin production begin. Retention of the diaphragm for 12–18 hours may be relatively safe, whereas prolonged to 36 hours or more without replenishing the spermicide may increase the risk of toxin-mediated disease.

Schwartz *et al.* evaluated the use of barrier contraceptives as a risk factor for non-menstrual toxic shock syndrome. Potential risk factors for non-menstrual TSS were compared for 28 patients and 100 age-matched controls. Use of barrier contraceptives was associated with a significantly increased risk of non-menstrual TSS, with matched odds ratios of 10.5 and 11.7 for contraceptive sponge and diaphragm use, respectively. Use of non-barrier contraceptive methods was unrelated to non-menstrual TSS. Despite the elevated odds ratio, the incidence of non-menstrual TSS in barrier contraceptive users and the risk of non-menstrual TSS attributable to barrier contraceptive use are low.

CLINICAL PRESENTATIONS

Toxic shock syndrome is a multisystem illness (Table 72.2). A syndrome consisting of malaise, myalgia, low-grade fever, nausea, vomiting and/or diarrhea may antecede overt disease. In the full-blown, acute systemic illness, the patient presents with fever (greater than 38.9ºC or 102ºF), sore throat, headache, chills, severe hypotension, myalgia, pharyngitis, conjunctivitis, leukocytosis, and generalized arthralgia. The rash is usually a consistent part of the syndrome and presents as a diffuse ‘sunburn-like’ blanching macular erythema. Neurological symptomatology, when present, is usually severe.

Cerebrospinal fluid analyses, when done, are within normal ranges. The patient complains of headache. Disorientation, confusion, agitation, and photophobia are not uncommon. A small bowel type of watery diarrhea is common in these patients. Diffuse myalgia occurs in the great majority of patients such that they may complain of marked skin and muscle tenderness when touched or moved. Other musculoskeletal symptomatology involves arthralgia of the hands and knees. In rare cases, sterile knee effusions and synovitis of all the metacarpal, phalangeal and proximal interphalangeal joints may be present.

Profound hypotension is one of the characteristic findings of full-blown TSS. A number of abnormal laboratory findings may be observed. The white blood cell count is generally elevated but may be normal. A large left shift in the neutrophil series occurs but may not be present on the first day of illness; toxic granulation and Dohle bodies are often found and may be an important diagnostic clue. Urinalysis usually shows pyuria (5–10 white blood cells per high-power field) and proteinuria, but cultures (in the absence of an unrelated urinary tract infection) are sterile. Gram stains of vaginal or cervical secretions generally show polymorphonuclear leukocytes and very sparse Gram-positive cocci in singlets, doublets, or clumps. Moderate elevations in liver function tests are common, and the serum amylase may be elevated. Most patients have elevations in the blood urea nitrogen (BUN) and creatinine and a few have required dialysis. Elevation of the creatinine phosphokinase (CPK), often dramatic, may occur. Severe illness may be accompanied by other findings. The platelet count often drops below 100000/mm^3 in the first week of illness, and disseminated intravascular coagulation uncommonly occurs.

Electrocardiogram abnormalities include sinus or supraventricular tachycardia, non-specific ST segment changes, and first-degree heart block. T-wave inversion is sometimes recorded in the precordial leads as are funnel branch, premature atrial and ventricular extrasystole.

Patients with TSS may have evidence of pulmonary involvement which may be mild or progress to frank adult respiratory distress syndrome. The development of adult respiratory distress syndrome indicates a poorer prognosis for these patients. On the fifth to the twelfth day following the onset of illness, the patients will experience a danderous-like desquamation involving the face, trunk, and extremities. This is followed by a fullthickness peeling of the palms and soles of the feet (Figure 72.2). Despite the extensiveness of the process, healing is without scar formation. Vaginal examination in women with tampon-induced TSS reveals mucosal hyperemia with varying degrees of inflammation. A purulent, malodorous cervical discharge may be observed. Bilateral adnexal tenderness is not an uncommon finding.

NON-MENSTRUAL TOXIC SHOCK SYNDROME

Progressively more and more cases of TSS are occurring in non-menstruating women. The gravity of illness and the potential for increased mortality is such that obstetricians and gynecologists must be aware of those clinical settings in which disease may potentially occur (Table 72.3). In obstetrics, the syndrome has been described following vaginal delivery, Cesarean section, and spontaneous and therapeutic abortion. In the gynecological patient, disease has been documented as complicating surgical procedures,

such as tubal ligation, vaginal and abdominal hysterectomy, urethral suspension, bladder suspension, exploratory laparotomy and therapy of extensive condyloma acuminatum. TSS may occur in patients with meatitis, Bartholin's gland abscess, and acute salpingitis. Following abdominal surgery, a unique type of staphylococcal wound infection may occur. In contradistinction to traditional wound infection, where the onset of signs and symptoms is usually about the fourth day, disease usually begins as early as the second day. In the cases reported, local signs of wound infection were minimal or absent. The usual tip-off to the diagnosis of TSS is the development of

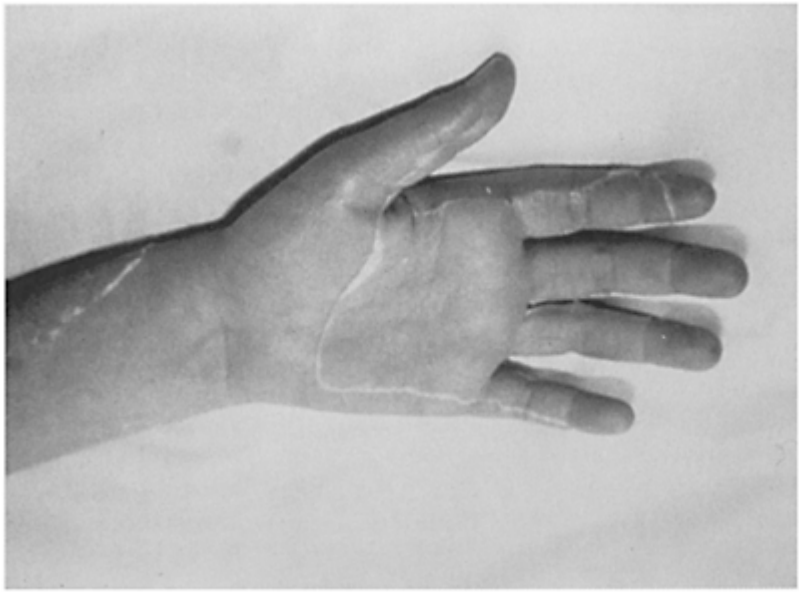

Figure 72.2 Palmar desquamation characteristic of toxic shock syndrome (Courtesy of the CDC)

Table 72.3 Obstetrical and gynecological conditions in which toxic shock syndrome has occurred

Category	***Conditions***
Surgical wound infections	Exploratory laparotomy Abdominal hysterectomy Urethral suspension Bladder suspension Dilatation and curettage Cesarean section Septic abortion

	Surgical removal of condyloma acuminatum
Non-surgical conditions	Vaginal delivery Diaphragm use Contraceptive sponge use Vaginal infections Pelvic inflammatory disease Viral influenza

watery diarrhea and a profuse erythroderma. The absence of local signs of a wound infection does not preclude the existence of staphylococcal infection at the operative site capable of producing TSS. The probability of the diagnosis of TSS is suggested by the development of the sunburn-like rash in conjunction with diarrhea and/or headache. These usually precede full-blown TSS.

DIAGNOSIS

Recognition and definitive documentation of TSS is difficult. The variability of the signs and symptoms of disease *(forme fruste)* and the large number of clinical conditions on which TSS may be superimposed have been significant impediments to early diagnosis, particularly in the non-menstruating, non-superabsorbent tampon user. There is no definitive test for TSS. The diagnosis is based on recognition of a constellation of signs and symptoms indicative of multi-organ involvement which meets the CDC case criteria. Any woman who becomes ill with fever, headache, diarrhea, myalgia or any combination thereof should be suspected of having TSS. The presence of a rash should greatly heighten the clinician's suspicion of TSS. The diagnosis of TSS early in the clinical course can be quite difficult because the disease can resemble other illnesses.

THERAPY

Proper management of women suspected of having TSS includes a careful vaginal examination, notation of vaginal lesions such as ulcerations, and removal of any tampons. A search for focal staphylococcal infections (boils, etc.) should be made. Blood cultures for *S. aureus* should be obtained. The initial therapy is that of aggressive volume replacement. Because of the large volume of fluids necessary, it is strongly recommended that a Swan-Ganz catheter be placed and Anesthesia be alerted that adult respiratory distress syndrome may develop in this particular patient.

Concomitantly, local therapy should be directed to remove as much toxin as possible from the portal of infection. In cases where the vagina has been the principal portal of infection, it is recommended that the vagina be thoroughly dried out using cotton drumsticks. Extensively irrigating with saline and then cleansing with hydrogen peroxide or betadine iodine are advocated, immediately prior to the institution of antimicrobial therapy. Antimicrobial therapy requires the administration of a beta-lactamase-resistant semisynthetic penicillin such as oxacillin or nafcillin. A single dose of netilmicin is advocated because of its synergistic effect with the semisynthetic penicillins. Because of

the probability of underlying renal damage, a second dose is rarely administered. The choice of netilmicin over gentamicin or tobramycin is based on its being the least nephrotoxic of all the aminoglycosides.

The patient should be extensively monitored for the development of renal failure and/or adult respiratory distress syndrome. The development of adult respiratory distress syndrome is a poor prognostic sign. Although bacteremia in TSS is a very rare event, when it does occur it has significant therapeutic connotations. Patients with documented bacteremia due to *S. aureus* should be treated for a minimum of three to four weeks with a combination of parenteral and oral therapy to preclude the delayed development of metastatic complications such as osteomyelitis or brain abscess. If adult respiratory distress develops, mechanical ventilation with a high FI O_2 and positive end-expiratory pressures from 5–15 cm of H_2O are often required. Patients who do not respond readily to fluid replacement are at high risk for multi-organ failure and should be immediately transported to centers which can effectively deal with tertiary complications involving lungs, kidneys, and other vital organs.

RECURRENT TOXIC SHOCK SYNDROME

Recurrence of TSS in cases related to menstruation has been reported to be as high as 34%. Retrospective data suggest that, with effective antistaphylococcal antibiotic administration, risk of recurrence is decreased to approximately 5%. The incidence of recurrence or relapse in non-menstruating cases is not known due to an incomplete database. Recurrences have been described in cases of TSS complicating surgical wound infections. These relapses were associated with recrudescence of the wound infection and incomplete eradication of the TSS strains of *S. aureus*. Eradication of the causative agent at the site of disease is mandatory to preclude relapse of non-menstruating TSS.

POSTINFLUENZA TOXIC SHOCK SYNDROME

An association between TSS and *S. aureus* pneumonia was first described in 1985. Pulmonary superinfection in cases of influenza is a well-recognized phenomenon. The decrease in polymorphonuclear leukocyte chemotaxis and tracheobronchial clearance which occurs in viral infection predisposes the organ to bacterial super-infection. With the development of an influenzal bacteria tracheitis, the strain of *S. aureus* may on occasion produce TSS symptoms.

Disease may provide conditions for toxin production that may not ordinarily be present for the same staphylococcal strain when merely colonizing the respiratory tract. What ensues is a syndrome of unexplained multi-organ failure which develops during the influenza season. The development of rash, disseminated intravascular coagulopathy, and multi-system failure are poor prognostic factors. The characteristic pattern of disease is the rapid onset of hypotension, scarlatiniform rash (followed by desquamation and recovery) and other serious manifestations of multi-organ system failure. Since treatment for TSS may be facilitated by drainage of local infection, it becomes imperative to look

for pneumonic empyema or sinusitis in all patients who appear to have TSS associated with influenza or upper respiratory tract infections.

TOXIC STREPTOCOCCAL SYNDROME

Close examination of cases of presumed staphylococcal TSS have revealed a multi-system disorder that shares many of the features of staphylococcal TSS, but is caused by toxins elaborated by group A beta-hemolytic *streptococcus*. Clinically the non-menstrual patients fulfill the criteria for the clinical diagnosis of TSS: fever, hypotension, multi-system dysfunction, and diffuse macular erythroderma followed by desquamation.

The TSS-like syndrome usually occurs in patients with severe soft-tissue infections due to *Streptococcus pyogenes* (group A streptococci); however, Herold reported a case of group A streptococcal toxic shock in a patient with only mild pharyngitis. Lersch *et al.* reported a case of a 33-year-old woman suffering from anal erosions who developed severe illness with fever, diarrhea, hypotension, acute abdominal pain, dyspnea, renal and hepatic impairment, myalgia, desquamation of the skin, leukocytosis, anemia, hypocalcemia, and decreased serum albumin and cholesterol levels. Exploratory laparotomy did not reveal pathologic findings. Hemolytic group A streptococci were grown from peritoneal swabs and pleural exudate in bacteriologic cultures. The patient slowly recovered after intensive penicillin and tobramycin therapy.

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73
Nosocomial infections

HISTORICAL PERSPECTIVES—PUERPERAL SEPSIS

The genesis of nosocomial infection resides within Obstetrics and Gynecology; more specifically with the problem created by the group A beta-hemolytic streptococci—puerperal sepsis.

Hippocrates is reputed to be the first person to recognize the association between puerperal fever and erysipelas:

> *'If erysipelas of the wound seize a woman with child, it will probably prove fatal.'*

The concept that erysipelas and puerperal sepsis were identical in terms of causative agents was first proposed by Claude Pouteau in 1760; however, its perception was delayed until 1795 when Alexander Gordon and Thomas Denman independently presented now classic theses whose focal point was the fact that disease was caused by contagion *per se* and was unrelated to other etiologies. Gordon's paper is the first real epidemiologic study of a nosocomial infection:

> *'The midwife who delivered #1 on the table carried the infection to #2 and to the next woman whom she delivered. The physician who attended #1 and #2 carried the infection to #5 and #6 who were delivered to him and to many others. The midwife who delivered #3 carried the infection to #4 and from #24 to #26 and successively to every woman who she delivered.'*

Denman wrote,

> *'It is a disagreeable declaration for me to mention that I myself was carrying the infection to a great number of women.'*

In his second paper appears the following:

> *'There are other consequences of epidemic or even sporadic puerperal fever which would be criminal to be sounded. This is the contagious nature of these fevers: having long been suspected but not fully proven they may be and often have been conveyed by midwives and nurses from one patient to another.'*

In the realm of therapeutics, the concept later to be advanced by Semmelweis is already to be found in the writings of Robert Collins. Following a long series of epidemics of puerperal fever at the Dublin Lying-In Hospital, Collins in 1729 introduced chlorine

disinfection and used the principles of fumigation. This sterile local scouring with chloride of lime (calcium hydrochloride) and sterilization of blankets resulted in the disappearance of puerperal fever. Unfortunately, after Collins's time his methods were discontinued and puerperal fever once again returned to Dublin Lying-In Hospital.

Probably the most assertive statement was ultimately to be written by Samuel Kneeland in 1846 in his paper, *The Connection Between Puerperal Fever and Epidemic Erysipelas, Its Origin and Modes of Propagation*.

> *'It may be propagated by direct inoculation with fluids of the living and the dead; by the effluvia arising from the bodies of the sick, inhaled in the very chambers of death (as in the wards of the hospital) and carried about by persons, physicians, by clothes, or by bedding floor mites which have been in contact with the diseased person.'*

Gordon, Denman, and Kneeland are historically overshadowed by Oliver Wendell Holmes and Ignaz Philipp Semmelweis. Their public dominance of the issue has been thought to be in part a function of the fact that they were both extremely young men at a time of intellectual sclerosis. Oliver Wendell Holmes had studied

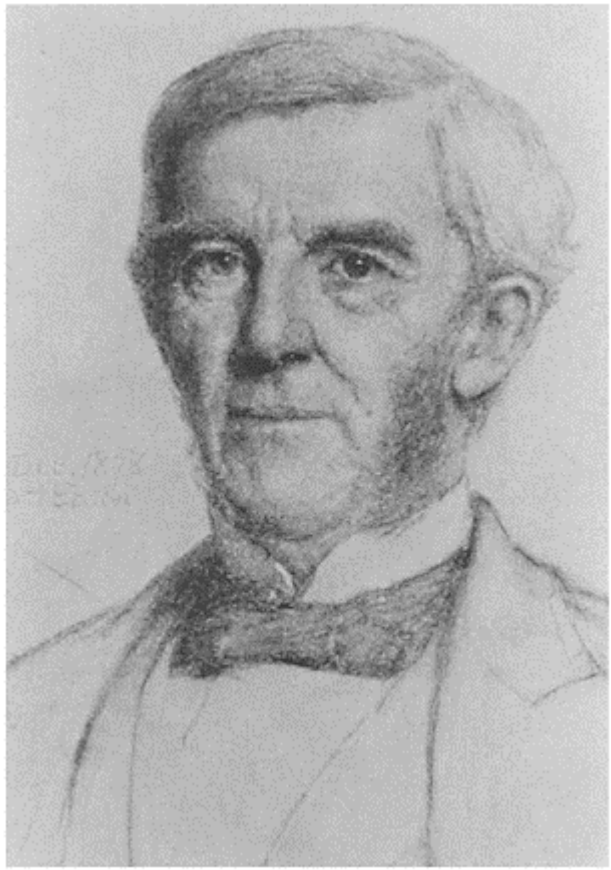

Figure 73.1 Oliver Wendell Holmes, MD (Courtesy of National Medical Library, Bethesda, Maryland)

medicine in France and was already familiar with the work of Gordon at the time his essay appeared in 1843 (Figure 73.1). While it failed to provide any new insight into the problem of nosocomial puerperal sepsis, it provoked violent outbursts, particularly from Hugh Lenox Hodge and Charles D. Meigs. Meigs in particular attacked the author for wrapping himself in *'the gratuitous and illusionary mantle of authority'*.

Semmelweis's contributions were published over the period of 1847–1849 (Figure 73.2). A major reason why the life and works of Semmelweis have attracted such wide attention was the result of the violent controversy precipitated in Austria and Germany. Semmelweis's premise emanated from the marked discrepancy in maternal mortality that he observed in two large divisions in Vienna General Lying-In Hospital. In the end,

Figure 73.2 Ignaz Philip Semmelweis, MD (Courtesy of National Medical Library, Bethesda, Maryland)

Semmelweis was destined to be his own enemy. He was never one to try honey on bees; an example is an open letter written to Professor Spaeth of the St. Joseph's Academy in Vienna who, in reviewing the obstetric literature of the preceding year for a medical yearbook (published on March 20, 1861), had described the cause of puerperal sepsis as being an inflammation of the fallopian tube. Semmelweis wrote:

> *'From these expressions of opinion Herr Professor has given me the impression that his spirit has not been lit up by the puerperal sun which rose in Vienna in the year 1847, although it shone so near to him.*
>
> *This stubborn ignoring of my doctrine, the stubborn ruminating over errors, causes me to bestow upon you the following explanation:*
>
> *I carry with me the consciousness that ever since the year 1847 thousands and thousands of lying-in women and sucklings have died who would not have died if I had not remained silent. But every error*

> *concerning puerperal fever which has been spread, the necessary corrections have been made.*
>
> *In this massacre you, Herr Professor, have participated. The homicide must cease, and with this objective of bringing this homicide to an end I will keep watch and every man who dares spread dangerous errors regarding puerperal fever will find in me an active opponent. For me there is no other means of checking the murder than unsparingly to unmask my opponent; and not one whose heart is in the right place will blame me for making use of these means.'*

The contributions of Holmes and Semmelweis had been sounded before. In reality they brought no new thoughts to the doctrines which had been developed. Yet we turn with reverence to these individuals. It is a reverence which is a homage in part to the powers of perception and logical thought, but in part to something else. The words of Holmes and Semmelweis were more than those of medical progress, they were the sounds of revolution. As Pasteur has pointed out, all revolutions, even those imposed by scientific demonstration, leave behind them the vanquished who do not forget easily. The something special for which we pay homage to these men is perhaps best expressed in a letter from Oliver Wendell Holmes to a Doctor Chadwich in 1883:

> *'I shouted my warning louder and longer than any of them and I am pleased to remember that I took my ground on the existing evidence before the little army of microbes was marched up to support my position.'*

Those well could have been words of Semmelweis had he not paid the ultimate price for revolution. Confined to a mental sanitarium, Semmelweis died on August 13, 1865, from the same infection that had fostered his intellectual revolution. On the middle finger of the right hand was an infected wound secondary to a gynecologic operation. Metastatic abscesses developed in the right armpit and ultimately invaded the pleura. The day before the death of Semmelweis, Joseph Lister in Glasgow, acting on his interpretation of selected writings of Louis Pasteur, used carbolic acid as an antiseptic in treating a case of compound fracture.

Figure 73.3 Louis Pasteur (Courtesy of National Medical Library, Bethesda, Maryland)

Semmelweis was a mixture of a high sense of morality coupled with the guilt engendered by his unknowing participation in what he had termed ‘a massacre’. He was a man haunted by that knowledge.

The ultimate demonstration of causalities was to be Pasteur’s (Figure 73.3). The proclamation of this discovery was typical of the man. The date was March 11, 1879. On that day one of Pasteur’s dipoles was expounding on the causes of epidemic puerperal fever in lying-in hospitals. Apparently at a saturation point, Pasteur interrupted him.

> *‘None of these things caused the epidemic. It has been nursing and medical staff who carried the microbe from an infected woman to a healthy one.’*

In ensuing debate the speaker retorted that the microbes would probably never be found. Pasteur, not replying, merely limped to the blackboard and drew a picture of a chainlike organism. *'There, that is what it is like.'* Pasteur had found the streptococci located in the bloodstream of women dying with puerperal sepsis. Thus the page was turned and a new chapter begun.

FACTORS PREDISPOSING TO NOSOCOMIAL INFECTIONS

The concept of nosocomial infections had its genesis in the discovery of the bacterial nature of diseases and the demonstration of the contagiousness of selected diseases, in particular, that due to group A beta-hemolytic streptococci.

The major catalytic event for the perception of nosocomial infections was the creation of hospitals, particularly lying-in hospitals. A prime example is the first series of epidemics of puerperal sepsis which occurred in Great Britain. These were seen in the years 1760 and 1761, shortly after the opening of maternity hospitals. The recognition of the communicability and contagiousness of infections in the hospital environment contributed to the governing concept of cleanliness, sterile surgical techniques, and aseptic wound care.

The advent of effective antimicrobial therapy has had a major effect in redefining nosocomial infections. The initial emphasis placed on exogenous pathogens has progressively shifted in terms of the spectrum from exogenous to endogenous pathogens. The bacterial flora that is dominant within hospital environments results from Darwinian-like pressures induced by antibiotics. A prime example is the problem of the multi-drug-resistant klebsiella. When patients are prospectively monitored for the presence of the multi-resistant klebsiella organisms which are responsible for endemic nosocomial infections, 50% of those who become intestinal carriers of the organism during their hospitalization subsequently develop infection, in contrast to approximately 10% of those who do not become intestinal carriers. The prime predisposing factor to intestinal colonization with klebsiella and to exertion of the selective pressure in favor of the multi-drug-resistant organism is antibiotic administration. The acquisition of nosocomial strains and their colonization appears to be an important intermediary step in the development of nosocomial infection and serves to perpetuate a significant reservoir of organisms within the hospital.

Augmented technology has radically altered the complex set of circumstances which govern a hospital environment. The newer surgical and anesthetic techniques which have developed now allow for more complex procedures, performed on progressively more debilitated patients. With the introduction of more sophisticated parenteral fluids for hyperalimentation and the necessity for prolonged administration has come a new set of problems. All of these factors have contributed to the changing spectrum of nosocomial infection.

Nosocomial infection is often an interplay between host defense mechanisms and organismal virulence. The patient prone to nosocomial infections is in many instances preselected by an earlier alteration of the host defense mechanisms due to irradiation, antimetabolite therapy, previous antibiotic therapy, or the administration of corticosteroids. What distinguishes obstetric or gynecologic patients from their

counterparts on the medical wards, in terms of nosocomial infection, is that with the exception of gynecologic patients undergoing therapy for a malignancy of the female genital tract, one is dealing with a normal individual in whom the placement of foreign bodies or iatrogenic surgical disruption of cutaneous or mucosal barriers selects for nosocomial infection.

Unlike many areas in which nosocomial infections function, in obstetrics and gynecology the immunologic status of patients is rarely a prime selecting factor. The principal problems which obstetricians and gynecologists deal with are those associated with basic procedures, such as the use of indwelling intravenous catheters, intra-arterial catheters, intravenous hyperalimentation lines, arteriovenous fistulae (hemodialysis patients), cerebrospinal fluid shunts, presence of urinary catheters or wounds, prior or ongoing antibiotic therapy and/or presence of an identifiable cutaneous infection. Since the effect tends to be additive, often more than one factor is implicated in the pathogenesis of a given infection.

URETHRAL CATHETER-ASSOCIATED INFECTIONS

Stephen R.Zellner, MD

Approximately 5% of patients admitted to general hospitals in the United States will develop a nosocomial infection. Infections of the urinary tract account for approximately 40% of these infections, or roughly 3% of all hospital admissions. Usually these infections are the result of catheterization, instrumentation, or urinary tract surgery.

Among the portals of entry by which bacteria may gain access to the catheter system and ascend to the bladder are the urethral meatus and periurethral space, the junction between catheter and drainage tube, the junction between drainage tube and collection receptacle, and the drainage receptacle. To minimize the infection related to bladder catheterization, special attention has been given to maintaining asepsis of the catheter and drainage system.

Bacteria enter the bladder by migrating through either the periurethral space or the catheter lumen. The sheath of exudate lining the urethra and surrounding the catheter provides an excellent culture medium for bacteria.

The application of antibiotic ointments to the external urethral meatus, catheters impregnated with antibiotics, antibiotic-containing lubricants, and more recently, iodophore-containing lubricants have been used in attempts to decrease bacterial colonization of the periurethral space.

However, double-blinded studies have demonstrated that such lubricants and impregnated catheters had no effect on the subsequent development of urinary tract infection (UTI). Most catheter-associated UTIs occur after the second day of use, by which time the antibiotic-antiseptic combination has been carried away by the flow of urine and mucus and is no longer available.

Closed urinary drainage

Much effort has been expended toward developing a system of catheterization that prevents or at least decreases the hazards of infection associated with indwelling urethral catheters.

Once the catheter, tubing, and drainage receptacle have been aseptically placed, the integrity of the system must not be violated. That is, the system should be both initially and permanently a closed one. Several years ago it was demonstrated that the frequency of catheter-associated infections could be reduced with a closed drainage system. Fewer than 10% of patients placed on a closed system of drainage developed bacteriuria when catheterized for periods between 1 and 14 days. In contrast, 90% of patients employing this closed system became infected when asepsis and the integrity of the system were broken by disconnecting the drainage tube from the catheter.

Closed systems employing catheters impregnated with antibiotic agents or lubricated with antibacterial-containing gels are of no benefit over a carefully maintained closed drainage system. These antibacterial materials are water-soluble and after catheter use for 24–48 hours are no longer available or effective. Since most catheter-associated UTIs develop between the second and fourth day of use, this maneuver adds little to a carefully inserted and maintained closed drainage system.

Use of antibiotics in association with closed urinary drainage

Although investigators have been unable to demonstrate any beneficial effect from the systemic administration of prophylactic antibiotics to patients on open catheter drainage, in patients on closed catheter drainage the therapeutic use of antibiotics has shown some promise. In an open system that permits ready access of organisms to the bladder, the emergence of resistant strains in patients treated with antibiotics frequently occurs. A closed system, however, provides a barrier to reinfection. Using systemic antibiotic agents with demonstrated effectiveness against the infecting organism by *in vitro* testing, 48% of patients in one study, admitted to the hospital with bacteriuria and placed on a closed system of catheter drainage, were cured. Unfortunately, in only 30% of the group of patients who developed a nosocomial bacteriuria while on catheter drainage was the infection resolved. Removal of the foreign body from the bladder and

Table 73.1 Effectiveness of bladder irrigation in preventing bacteriuria in catheterized patients*

Catheter Group	*Protection (%)*	*Infection (%)*
Open drainage	0	100
Open drainage+saline irrigation	0	100
Open drainage+ systemic antibiotics	25	75
Closed drainage	77	23
Triple lumen+acetic acid rinse	80	20

Triple lumen+ nitrofurazone rinse	80	20
Triple lumen+ neomycin-polymyxin B rinse	94	6

*Abacteriuric patients requiring indwelling catheter drainage for 10 days or less (Andriole VT. In Kaye D, ed. *Urinary Tract Infection and Its Management*. St. Louis: Mosby, 1972)

institution of appropriate antibiotic therapy is of course ideal. In patients in whom this approach is not feasible, systemic antibiotic therapy and careful maintenance of a closed drainage system will be beneficial.

Role of bladder irrigation with closed urinary drainage

Techniques of bladder irrigation have been employed in an attempt to decrease the migration of bacteria through the catheter lumen. The ideal irrigation solution should be non-toxic, active against both Gram-positive and Gram-negative organisms, inexpensive, non-absorbable, and easy to use, and should have a low incidence of acquired bacterial resistance.

While such irrigation solutions can decrease the incidence of catheter-associated UTI (Table 73.1), many physicians do not use this technique as originally described—continuous drip through a triple-lumen Foley catheter. The central lumen drains the bladder contents, the second permits continuous instillation of fluid into the bladder, while the third provides for inflation of the balloon at the proximal end of the catheter.

Recommendations and techniques

From the preceding discussion one can only conclude that the insertion of a urethral catheter is not a harmless procedure. Despite sound technique, the insertion and prolonged use of an indwelling urethral catheter, if not properly managed, may result in urinary infection. This iatrogenic infection can predispose patients to the development of acute and chronic pyelonephritis, Gram-negative septicemia, and premature labor. Control of infection in patients on catheter drainage is the responsibility of everyone associated with patient care. Previously discussed concepts can be directly applied to techniques of catheter care for use in hospitals:

(1) Aseptically inserted sterile closed urinary collection systems can reduce the rate of development of significant bacteriuria from 100% to 21% at 7 days' exposure.
(2) A sterile three-way closed catheter system employing bladder irrigation with neomycin-polymyxin B solution can further reduce the incidence of bacteriuria to about 6%.
(3) Concomitant treatment with systemic antibiotics for patients with indwelling urethral drainage systems does not significantly reduce the incidence of bacteriuria.

Guidelines that can be easily adapted for use by all hospitals are necessary. One possible set of recommendations for the control of catheter-associated bacteriuria is presented for consideration.

(1) The potential risks and attendant morbidity associated with urinary catheterization should always be considered prior to placing the catheter. Indwelling catheters should be avoided unless absolutely necessary for the medical well-being of a patient. They should never be used solely as a matter of nursing convenience and should be discontinued promptly when they are no longer necessary.
(2) Insertion of an indwelling catheter should be done only by trained personnel using sterile techniques.

Materials required to perform the catheterization should be assembled beforehand. Sterile gloves, perineal antiseptic, sterile catheter, closed drainage collecting system, and sterile water-soluble lubricating jelly can be purchased in kit form or assembled by the hospital pharmacy.

Following careful and thorough scrubbing of the hands, sterile gloves are put on. Using one hand, designated as non-sterile, the clinician spreads apart the labia, exposing the urethral meatus. Adequate lighting and having the patient in the correct position greatly facilitate this maneuver. While adequate visualization is maintained, the urethral meatus is cleansed with antiseptic solution. Solutions of 1:1000 aqueous benzalkonium chloride (Zephiran) are not suitable for this purpose because they are frequently contaminated with Gram-negative organisms. An iodophore solution should ensure adequate perineal and meatal antisepsis. Cleansing of the perineum should be in the direction of urethra to rectum, never the reverse. The indwelling catheter should be coated with lubricating jelly and slowly threaded through the urethra into the bladder. Lubricants and catheters impregnated with antibiotic compound may be used; however, their efficacy is questionable. The proper-sized catheter should pass easily so as to avoid urethral irritation, yet be of sufficient lumen diameter to permit unimpeded bladder drainage. The catheter should never be forced during insertion since this too causes unnecessary urethral trauma. Following the return of urine through the catheter lumen, the balloon is inflated with sterile saline and the catheter is taped to the patient in order to decrease its motion. The sterile drainage system is connected and attached at the patient's bedside.

(3) A sterile closed drainage system with a disposable clear plastic bag and connecting tubing should be used. The system should permit drainage of urine without disrupting sterile continuity. Currently used collecting bags are fitted with a drain spout at the most dependent portion of the bag to allow evacuation of the container without violating the integrity of the system.

Samples of the urine needed for analysis may be withdrawn from the soft rubber portion of the catheter much as one would perform a venipuncture. The area is

prepped with an alcohol sponge, a needle attached to a syringe is inserted, and the urine is aspirated.

Catheters and closed drainage systems that have been inserted aseptically require replacement only if they malfunction. Failure to drain readily or the presence of intraluminal sand or concretions are indications of impending catheter obstruction.

(4) Second only to aseptic insertion of the catheter in importance is a program of daily catheter care:

(a) The junction of the catheter with the drainage tube must not be broken once it is connected.
(b) Collecting bags should be drained at least every 8 hours. Care must be taken not to contaminate the mouth of the spigot or permit reflux of urine into the collecting tube.
(c) Bags may be hung at the bedside, on chairs, or on stretchers but must never be raised above the bladder level.
(d) Twice-daily washing of the perineum with soap and water is recommended so as to detect early meatal irritation and catheter malfunction.
(e) When possible, patients with indwelling catheters should be cared for in separate rooms to avoid crowding. Strict attention must be given to hand-washing before and after contact with each patient or catheter system.

(5) Catheters should not be irrigated unless this is specifically ordered by the physician.

The sole indication for a single irrigation of a closed drainage system is obstruction of urine flow, usually due to clotted blood. Routine intermittent irrigation is felt by most investigators to be of no value in preventing UTI. Specifically, simple flushing of the system permits only a short contact time between organism and antibacterial agent and does not provide adequate time for killing it. In addition, in order to perform intermittent irrigation of the bladder, the junction of the catheter and drainage tube must be broken, increasing the risk of infection.

Prophylactic continuous irrigation should only be used after the development of an efficient system of sterile closed drainage. Irrigation may then be added to improve bladder care.

(6) All indwelling catheters, regardless of the length of time they are to be used, must be routinely attached to a closed system of drainage.

(7) All patients on bladder drainage must be closely monitored for the development of UTI. Daily routine culturing by either nursing personnel or the hospital epidemiologist is acceptable. Prompt reporting of culture data to physicians is critical if the program is to be effective.

Treatment of infections in catheterized patients

Bacteriuria in a previously abacteriuric patient requiring indwelling closed catheter drainage often reflects breaks in catheter care techniques. Antimicrobial therapy is reported to be effective in about 30% of patients in whom closed catheter drainage is continued. Reinfection and failure to respond to the administered therapeutic agent

frequently make removal of the catheter system necessary. Only when antimicrobial therapy is combined with efficient urethral catheter management can UTI in patients with indwelling catheters be resolved.

Antibiotic preparations effective in the treatment of UTI have already been mentioned. In patients requiring long-term catheterization, suppressive therapy with methenamine salts and urine acidification, with nitrofurantoin or with nalidixic acid, may be beneficial once the acute infection is controlled.

Acquired bacteriuria in patients with short-term indwelling urethral catheters can be promptly detected by frequent bacteriologic monitoring. Appropriate antimicrobial therapy can then be selected on the basis of *in vitro* sensitivity tests, and an antimicrobial agent to which the organism is sensitive can be administered.

INFECTION FROM INTRAVENOUS INFUSIONS OR FEEDINGS

Gilles R.G.Monif, MD

One of the major technologic advances has been the ability to utilize the intravascular compartment. The ease with which fluids and drugs can be given may, on occasion, engender a certain amount of laxity. Often forgotten is the concept that a major host defense mechanism, the cutaneous barrier, has been penetrated iatrogenically and transiently bridged with a foreign body.

With the increasing use of the indwelling intravenous catheter has come a concomitant increase in both local and systemic infectious complications. Intravenous catheters now rank as one of the leading causes of septicemia in hospitalized individuals. The reported incidence of infection ranges from 0.4% to 2%. The principal factor selecting for infection is the duration of time that the catheter is left in place. The longer the time interval, the greater the risk of catheter-related infection and septicemia. The intravenous catheter should be used only when absolutely necessary -not merely for the convenience of the housestaff and paramedical personnel.

If the catheter tip is serially cultured, it is found to be progressively colonized by bacteria endogenous to the skin flora. There is a very poor correlation between the recovery of organisms from the catheter tip *per se* and the occurrence of septicemia, and between the incidence of phlebitis and septicemia. The lack of correlation emanates from the fact that in many instances the solution used is non-physiologic in terms of pH or that selected antimicrobial agents are extremely sclerosing (e.g. erythromycin, cephalosporins).

While there is little correlation between phlebitis and septicemia (1%), the converse is not true. Patients with catheter-induced septicemia very often have evidence of phlebitis. The prime pathogens are *Staphylococcus aureus* (penicillin-resistant) and *Candida albicans*.

When polyethylene and siliconized catheters are used preoperatively in seriously ill patients requiring long-term administration of intravenous fluids, the catheter should be changed 48 hours after insertion. At this time the choice of cannula becomes important. In patients requiring long-term administration of intravenous fluids, a progressive march up the arm and the initial use of a scalp vein needle is preferable to using a plastic catheter. Scalp vein needles are in general associated with a lower rate of septicemia and

phlebitis than plastic catheters (provided they are not subjected to prolonged use). Because the scalp vein needles are not as securely held as plastic catheters, they often require replacement, indirectly contributing to the reduction in iatrogenic infectious morbidity.

Location of intravenous site

The arm is the preferred site for short-term intravenous therapy. With patients requiring long-term intravenous therapy, it is advocated that large veins be utilized, particularly when there is the possibility that hypertonic nutrient solutions will be administered. If one uses such a major portal, daily catheter care should include:

(1) dressing removal;
(2) skin cleansing with an antiseptic; and
(3) restoration of the sterile dressing.

When antibiotics or other intravenous medications are administered through alimentation lines, great care must be given in terms of the compatibility of the various solutions being administered. Otherwise, precipitation due to physical or chemical incompatibilities may result. If blood samples are required, they should be taken from separate intravenous sites, not from the catheter.

Preparation of intravenous site

The preparation of the site of vena puncture is important and should not be neglected. Guidelines for sterilization of a vena puncture site include vigorously cleansing the site with tincture of iodine, 70% alcohol or tincture of chlorhexidine (0.5% in alcohol). Allow the area to dry for 30 seconds. Local application of topical antibiotics does not alter the incidence of catheter septicemia but does influence the frequency of local catheter-related infections (Table 73.2).

Table 73.2 Impact of vascular catheter site antisepsis on local catheter-related infection

Regimen—daily application	*Incidence of local catheter-related infection*	*Catheter septicemia*
No topical agent	6.5%	0.7%
Iodophor ointment	3.6%	0.7%
Polymixin, neomysin and bacitracin*	2.2%	0.7%

Maki DG, Band JD. *Am J Med* 1981; 70:739
*for antiseptics to exert their maximal benefit on catheter, the catheter must remain in place over four days

Maintaining the intravenous catheter

The intravenous catheter should be fixed to prevent a to-and-fro motion and possible catheter embolization. It is advisable to cover the site with a sterile dressing. The local application of a non-sensitizing local antibiotic cream is of questionable benefit in reducing the incidence of local or systemic infectious complications (Table 73.2). The intravenous site must be inspected daily. If evidence of local inflammation at the site of penetration or phlebitis is detected, the catheter must be removed. The earliest sign of phlebitis is pain on palpation. Often the patient will be the person who draws the physician's attention to this symptom.

One of the most common mistakes is attempting to re-establish patency of a catheter which has become occluded or is malfunctioning by manipulation or forced irrigation. Malfunction of a catheter is an indication for its removal. In those instances when the use of sclerosing solutions is anticipated, it is advisable to use small amounts of heparin, unless this is contraindicated, to avoid thrombophlebitis.

The incidence of catheter-related septicemia can be markedly reduced by replacing all catheters within a final time frame. The type of catheter influences the maximum duration of utilization (Table 73.3).

The rules governing the intravenous administration should be:

(1) Anticipate changing intravenous administration sets.
(2) Scalp-vein needles rather than short plastic cannulae should be utilized when long-term intravenous

Table 73.3 Avoidance of catheter-related septicemia by appropriate replacement

Type of intravenous catheter	*Maximum duration of utilization*
Venous	2–3 days
Arterial	4–5 days
Central	Can use over a prolonged period if daily care provided

Maki DG, Band JD. *Am J Med* 1981; 70:739
*Distance from skin to vessel wall influences time sequence for the acquisition of infection

administration is required. The risk-per-day of developing phlebitis is significantly greater at all times after the second day.
(3) Tenderness at the needle or catheter site and extending up the vein is an indication for immediate discontinuation of use of that specific site.

Whether or not daily applications of topical polymixin, neomycin and bacitracin ointment to the catheter site are warranted is still under analysis.

Diagnosis

The diagnosis of nosocomial infection due to multiresistant bacteria emanates from the microbiology laboratory. Once such an organism is identified the problem is two-fold:

(1) therapy of the individual patient; and
(2) eradication of the bacteria from the hospital environment.

By definition, the antimicrobial therapeutic options are limited. Often the physician is committed to the use of drugs with narrow therapeutic margins. Even more important is the 24–36 hour delay incurred by virtue of empiric commitment to an ineffective antimicrobial therapy. Nosocomial infection due to multi-resistant bacteria (MRB) is a precarious situation for both patient and hospital.

The two major areas where MRB function in Obstetrics and Gynecology are the surgical intensive care unit and the neonatal intensive care unit.

The major bacteria involved are the methicillin-resistant *Staphylococcus aureus (MRSA), Staphylococcus epidermidis* and the *Enterobacteriaceae*.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

Since the first reports of significant outbreaks of MRSA in hospitals in the United States, the prevalence of MRSA colonization and infection has increased not only in acute and chronic care facilities, but also in outpatient clinics which serve community-based populations.

The emergence of resistance to antibiotics has not been accompanied by an alteration of virulence. MRSA strains cause life-threatening infections, but they are no more pathogenic than methicillin-sensitive strains (MSSA).

The problems posed by MRSA strains are threefold:

(1) incorrect or missed identification of MRSA and, hence, inappropriate or ineffective antibiotic therapy;
(2) inappropriate antibiotic use despite adequate identification; and
(3) nosocomial spread within a healthcare unit.

MRSA isolates contain what is termed mecA gene, a 2130 bp stretch of DNA of non-staphylococcal origin which, together with a longer block of ‘foreign’ DNA, is incorporated into the staphylococcal chromosome. The mecA gene encodes for the 78 KD penicillin-binding protein (PBP) 2A which has very low affinity for betalactam antibiotics. It is generally assumed that PBP 2A acts as a surrogate enzyme which takes over the task of cell wall synthesis from the normal complement of staphylococcal PBPs.

An intact mecA gene component alone does not appear to fully account for phenotype resistance. Additional chromosomal sites outside of the mecA determinant locus appear to determine the MIC value of an MRSA isolate. The auxiliary genes co-function with the mecA gene in bringing about the high level beta-lactam resistance.

Microbiological identification of MRSA

A number of conditions can affect the results of disk diffusion, broth dilution, and agar screening from MRSA. In the near future, DNA detection methodologies may replace susceptibility testing in the identification of MRSA.

Inappropriate antibiotic therapy

MRSA strains of the 1990s are significantly different from the MRSA strains which existed in the 1960s and 1970s. The pattern of resistance is significantly broader and encompasses some antibiotics like clindamycin, imipenem, the newer aminoglycosides, and some of the new generation tetracyclines. The only antibiotic for which efficacy can be projected with reasonable certainty is vancomycin.

Nosocomial spread

Once introduced into a health care unit and allowed to colonize patients, both sporadic and epidemic outbreaks of MRSA may occur. When the units involved are newborn intensive care units, postoperative care units, and intensive care units, the character of the patient population magnifies the morbidity and mortality of MRSA. Traditionally, cases of MRSA infection were due nosocomially to internal antibiotic pressures. Because of the aggressive use of antibiotics in nursing homes, this patient population, when subsequently hospitalized, has proved to be a significant vehicle for unit colonization. MRSA prevalence rates as high as 34% have been reported from long-care settings. Currently, MRSA is in the community.

Management of wound sepsis due to MRSA

Once a MRSA isolate is identified, both active surveillance and control measures need to be implemented. Transmission occurs primarily from colonized or infected patients to others via the hands of healthcare personnel. Efforts to prevent the occurrence of new cases centers on active surveillance to identify the existent patient reservoirs of MRSA and the institution of control measures to block further transmission from any reservoir. Therapy requires both local wound care and antibiotic therapy.

The following sequence is recommended:

(1) notify infection control of an MRSA isolate;
(2) institute hand care (povidone, iodine, or chlorhexidine) and barrier protection;
(3) isolate the patient from other individuals who may be at potential risk for localized infection;
(4) debride wound and institute appropriate local care;
(5) administer intravenous vancomycin; the end-titration point for parenteral administration should be a patient who is afebrile for 24 to 36 hours and negative wound culture for MRSA;
(6) infection control should:

(a) survey patients in the immediate vicinity and those cared for by nurses involved with the pilot case for nasal MRSA colonization;
(b) survey all involved health care personnel for nasal carriage of MRSA;

(7) because the patient has both wound infection and wound sepsis (fever), parenteral vancomycin therapy should be implemented along with aggressive wound care.

If multiple patients are colonized, these individuals should be segregated together until all have been discharged. No new additional patients should be admitted to that unit or room. If healthcare personnel are nasally colonized, consideration should be given to local nasal treatment with mupirocin. Elimination of nasal carriage is critical to the success of any rational control policy.

Selective screening of 'high-risk' groups will miss potential vectors of MRSA. The key to nosocomial control is not waiting until some arbitrary quota of MRSA isolates is identified but using the pilot case to address its existence with the same measures as if one were confronted with a mini-MRSA epidemic.

Mupirocin is a topical antimicrobial that appears to have some promise in dealing with MRSA colonization. The drug has been used to eliminate nasal carriage with local application. In a controlled trial, nasal carriage of *S. aureus* was eliminated in all subjects and when

Table 73.4 Patients at high-risk for colonization with MRSA

(1) Patients recently discharged from the hospital requiring antibiotic therapy.
(2) Patients admitted from a nursing home or comparable
(3) chronic care facility. Patients who develop staphylococcal disease while in an intensive care unit.
(4) Patients admitted with obvious staphylococcal disease when MRSA is identified in the community.

re-colonization eventually took place, only 29% relapse with the pre-treatment strain was evidenced. Hill and Casewell reported an MRSA outbreak at a London hospital. Standard infection control means had failed to prevent colonization and infection of more than 200 patients. They achieved epidemiological control using mupirocin. Of the 40 patients and 32 staff studied, 98.6% and 90.1% respectively were free of nasal MRSA after treatment. Widespread use of nasal mupirocin ointment resistance develops. Miller *et al.* analyzed mupirocin resistance among MRSA over a four year period in a large teaching hospital. Mupirocin resistance among MRSA increased markedly over this period (1990, 2.7%; 1991, 8.0%; 1991, 61.5%; 1993, 65%) in association with increased use of mupirocin ointment as an adjunct to infection control measures. Mupirocin is a valuable agent in the control of MRSA. The drug must be used judiciously.

Prevention

Monitoring for the possible MRSA introduction into the hospital environment is the key to MRSA control. Patients at high-risk for colonization with MRSA are listed in Table73.4.

Nasal culturing for MRSA needs to be done on these individuals. Multiple studies have shown that nasal carriers of *S. aureus* are at higher risk for *S. aureus* bacteremia than are non-carriers in the setting of an MRSA outbreak. Colonization by methicillin-resistant strains represents a greater risk than does colonization by MSSA and strongly predicts the occurrence of MRSA bacteremia. In a prospective cohort study, Pujol *et al.* screened with nasal swabs 488 patients admitted to an intensive care unit. Nasal staphylococcal carriers were observed until developments of *S. aureus* bacteremia, ICU discharge, or death. One hundred and forty-seven (30.1%) of 488 patients were nasal *S. aureus* carriers; 84 patients (17.2%) harbored methicillin-sensitive *S. aureus* and 63 patients (12.9%) methicillin-resistant *S. aureus*.

Nosocomial *S. aureus* bacteremia was diagnosed in 38 (7.7%) of 488 patients. Rates of bacteremia were 24 (38%) of the MRSA carriers, eight (9.5%) of the MSSA carriers, and six (1.7%) of non-carriers. After adjusting for other predictors of bacteremia by means of a Cox proportional hazard regression model, the relative risk for *S. aureus* bactermia was 3.9 (95% confidence interval, 1.6–9.8; p=0.002) for MRSA carriers compared with MSSA carriers.

Methicillin-resistant *Staphylococcus epidermidis*

The traditional concept of *Staphylococcus epidermidis* as a contaminant must be revised. It is now apparent that this bacteria can function as a major nosocomial pathogen. A physician can no longer dismiss the recovery of a coagulase-negative staphylococci as a mere contaminant. In many institutions, *S. epidermidis* is the most common causative agent of hospital-acquired infection. It is a major pathogen in catheter-related septicemia.

The major problem confronting clinicians is evaluating the significance of recovery of *S. epidermidis* obtained through central or peripheral venous lines of a patient who is potentially septic and distinguishing bacteremia from superficial cutaneous contamination. The significance of an isolate must be evaluated in the context of the clinical setting, clinical signs, total neutrophil count and, in the neonate, immature neutrophil to total neutrophil count ratio.

Nosocomial infection due to *S. epidermidis* is associated with clinical situations in which there is a foreign body implanted in the host, i.e. prosthetic cardiac valve, a cerebrospinal fluid shunt, or with prolonged use of an indwelling intravenous line.

The proper procedure for differentiating bacteremia from contamination is to obtain peripheral cultures and evaluate the patient for clinical symptoms or signs of sepsis. In adults, a good correlation exists between repeatedly positive central line cultures, clinical symptoms of sepsis and positive peripheral blood cultures. Clinical signs of associated coagulase-negative staphylococcal sepsis in infants are relatively nebulous. They include: apnea, bradycardia, lethargy, or signs consistent with necrotizing enterocolitis.

The question as to whether removal of the catheter is mandatory for eradication of infection is controversial. If an alternative venous access is available, prompt removal is advocated. The probability of successful therapy without removing the catheter is markedly reduced.

Management

The methicillinresistant strains of *Staphylococcus aureus* are uniformly resistant to the semisynthetic penicillinase-resistant penicillins and all the cephalosporins. Strains with this pattern of intrinsic resistance also acquire plasmid-mediated resistance to most other antimicrobials with anti-staphylococcal activity. *In vitro* sensitivity may be demonstrated to rifampin, trimethoprim-sulfamethoxzole and the new generation tetracyclines. Uniform susceptibility to vancomycin has been demonstrated.

Therapeutic intervention for *S. epidermidis* is complicated by antibiotic resistance of most nosocomial strains. Between 5 and 40 percent of septicemic strains are methicillin- or oxacillin-resistant. While strains will demonstrate susceptibility to cephalosporins *in vitro*, the response to this group of drugs is poor. Vancomycin is clearly the drug of clinical choice; however, a few vancomycin-resistant strains have been identified.

Vancomycin is active in a pH range of 6.5 to 8.0. While effective in low concentrations *in vitro* against most Gram-positive cocci and bacilli, the drug is bacteriostatic but not bactericidal for the enterococci in concentrations that can be safely achieved. There is no cross-resistance between vancomycin and other currently available antibiotics.

One of the unique problems associated with vancomycin administration is the so-called ‘red-neck syndrome’. Rapid intravenous administration of vancomycin produces a histamine-like reaction characterized by flushing, tingling, pruritus, tachycardia and an erythematous macular rash involving the face, neck, upper trunk, back and arms with sparing of the rest of the body. Systemic arterial hypotension may complicate the whole picture. The syndrome can be avoided by slow intravenous drug administration.

Once a strain of methicillin-resistant *S. aureus* or *S. epidermidis* becomes established as an endemic nosocomial pathogen, its eradication from the hospital environment is difficult.

BACTERIAL COLONIZATION OF NEWBORN INFANTS BY MULTI-RESISTANT *ENTEROBACTERIACEAE*

Bacterial colonization with multi-resistant *Enterobacteriaceae* or MRS strain, if it occurs, does so within the first three days. Neither the occupancy rate in the unit nor the clinical state of the infant seems to influence the colonization pattern significantly. Barring antibiotic therapy, the bacterial spectrum usually remains essentially the same with increasing age during the stay in the unit. While colonization is a relatively common occurrence, disease is not, which indicates that other factors, such as clinical state of the infant, are of greater importance for major infection than the pattern of bacterial colonization.

ERADICATION OF MULTI-RESISTANT BACTERIA FROM THE HOSPITAL

Disease due to multi-resistant bacteria occurs primarily in intensive care units. Respiratory therapy equipment, fiberoptic bronchoscopes, vascular catheters, arterial pressure monitors, scalp vein needles and gastrointestinal colonization, rather than environmental sources, constitute the major reservoirs for colonization and potential translation into disease. The rectum is the first and most consistently colonized site. Once a serious nosocomial outbreak has been documented, both personal and environmental sources must be cultured.

While colonization occurs within the first few days of admission to the NICU, disease, if it develops, usually does so late in the second week of hospitalization (10–12 days).

Eradication of multi-resistant bacteria from the NICU requires removing all environmental sources of bacteria, cohorting patients and staff into a bacteria-exposed group and a new patient group, giving meticulous care to hand washing between patients, and daily bacteriological surveillance of the new patient group.

The translation from colonization to disease is multifactorial. Factors which select for disease are: prematurity, prolonged hospitalization, multiple courses of antibiotic therapy, and the use of vascular catheters and/or central lines.

The primary microbial reservoir is the colonized patient. The major vehicle of dissemination is the hands of the medical personnel among others.

When a previously colonized or infected in-patient is readmitted to the hospital, appropriate microbiological surveillance is deemed indicated.

Management of nosocomial clustering of disease due to multi-resistant bacteria

(1) The affected unit should be closed to further admissions.
(2) All patients with known or suspected infection must be isolated (glove-gown-stool); their cohort contacts (by common nursing personnel) must also be separated physically from the rest of the non-infected part of the unit and assumed to be infected until proven otherwise.
(3) Any nursing personnel who have had contact with known or suspected cases must be restricted from further contact with presumed uninfected infants until the outbreak has been defined and controlled, and they have been proven culture negative. There is no objection to permitting them to care for culture-proven cases; however, they should not, under any circumstances, be assigned to adult outpatient care units.
(4) Upon establishment of the above control measures, an epidemiologic investigation, in accordance with the discussion above, seeking the factor or factors responsible for the outbreak should be carried out. This usually will permit the enactment of further, even more specific measures aimed at rapidly curtailing the epidemic. Handwashing before and after administering care to every patient must be strongly re-emphasized.
(5) Microbiologic surveillance of the patient population should be carried out and environmental culture studies performed after the above activities have been satisfactorily launched.

(6) Upon discharge of the affected cohort (and control of the outbreak), a thorough terminal disinfection of the involved area is advocated.

Management of the individual patient with multi-resistant bacteria

Once a patient is identified as being colonized by a multi-resistant Gram-negative bacteria, the individual is placed on 'antibiotic resistance precaution'. The guidelines include:

(1) Room: one or two beds, no roommate with drainage tubes or Foley catheter.
(2) Gowns: not necessary
(3) Masks: not necessary.
(4) Hands: must be washed on entering and leaving room, even when gloves are worn.
(5) Gloves: must be worn for all patient or secretion contact. Double gloving advocated if it is necessary to do endotracheal suctioning.
(6) Articles: must have own urine measuring cup. Discard all sections and contaminated articles in plastic bag.

Contemporary strategies to prevent and control multiple drug-resistant nosocomial infections continue to rely on traditional control measures

handwashing
bacterial surveillance
cohortation
isolation procedures

Table 73.5 Blood and body fluid precautions

(1) Blood and other specimens should be labeled prominently with a special warning, such as 'Blood and Body Fluid Precautions' along with the lab or specimen sheets. If the outside of the specimen container is visibly contaminated with blood or body fluids, it should be cleansed with household bleach and water (1:10 dilution). Clorox solution should be mixed and labeled for this purpose. All blood specimens should be placed in a second container, such as an impervious bag, for transport. The bag or container should be examined carefully for cracks or leaks.

(2) Pap smear slides should be labeled with a 'Precaution' label and placed in an empty Pap smear box that is also labeled. The box should then be placed in an impervious bag and taken to the lab. Remember to label the Pap requisition with 'Blood and Body Fluid Precautions'.

(3) Blood spills, body fluids and secretions should be cleaned up promptly with a disinfectant solution of household bleach and water. Disposable gloves should be worn.

(4) Infectious waste hampers should be utilized for disposal of infectious waste (excluding sharps, liquid body wastes, linen or instruments). Lined infectious waste hampers with infectious waste bags on the inside and clear autoclave bags on the outside are advocated.

(5) All contaminated linen should be placed in a water-soluble bag first and then into the nylon linen bag which is then taken to the area's respective dirty linen room.

(6) Examination tables should be wiped down (using the Clorox solution in between patients when soiled with body secretions or fluids.

Table 73.6 Contact precautions

(1) Hands should be washed with antimicrobial soap (e.g., Betadine, Hibiclens) and water before entering and leaving room and, if wearing gown and gloves, after removing them.
(2) Hands should be washed thoroughly and immediately if they become contaminated with blood or body fluids.
(3) Avoid contact of open skin lesions with materials from HIV-positive patients. Wear gloves if lesions are present.
(4) Gloves should be worn when handling blood specimens, blood-soiled items, body fluids, excretions, and secretions, as well as all surfaces, materials, and objects exposed to them (e.g. vaginal discharge, amniotic fluid).
(5) Gowns should be worn when clothing may become soiled with body fluids, blood, or excretions.

to interrupt serial transmission of endemic pathogens in hospitals.

CDC GUIDELINES-UNIVERSAL PRECAUTIONS

Since medical history and examination cannot reliably identify all patients infected with human immunodeficiency virus (HIV) or other blood-borne pathogens, blood and body fluid precautions should be consistently used for all patients (Tables 73.5, 73.6 and 73.7).

(1) All heathcare workers should routinely use appropriate barrier precautions to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. Gloves should be changed after contact with each patient.
(2) Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other bodyfluids. Hands should be washed immediately after gloves are removed.
(3) All heathcare workers should take precautions to prevent injuries caused by needles, scalpels, and other sharp instruments or devices during procedures; when cleaning used instruments; during disposal of used needles; and when handling sharp instruments after procedures.
(4) Although saliva has not been implicated in HIV transmission, to minimize the need for emergency mouth-to-mouth resuscitation, mouthpieces or other ventilation devices should be available for use in areas in which the need for resuscitation is predictable.
(5) Heathcare workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care equipment until the condition resolves.

Table 73.7 Biosafety policy and procedures for the handling and transportation of blood and biological fluids

(1) All specimens are transported in sealed plastic bags.
(2) Leaking specimens are discarded immediately.
(3) Needles are never clipped, bent, or recapped after use. Immediately after use, needles and syringes are placed in special puncture-resistant containers.
(4) Clinic personnel wear gloves whenever handling blood or body fluid specimens, regardless of the patient's diagnosis. Individuals with cuts or other lesions on the hands must protect the affected areas with finger cots or gloves at all times while working in the laboratory.
(5) Masks, gowns, and protective eye coverings are required only in unusual circumstances when splashing is considered likely.
(6) Any employee who has had an accidental exposure to blood or other potentially infectious material is referred to the Employee Health Service for examination, further testing, and treatment as needed (e.g., hepatitis B immune globulin).

(6) Pregnant heathcare workers are not known to be at greater risk of contracting HIV infection than heathcare workers who are not pregnant.

PROVISIONAL PUBLIC HEALTH SERVICE RECOMMENDATIONS FOR CHEMOPROPHYLAXIS AFTER OCCUPATIONAL EXPOSURE TO HIV

Appropriate exposure management is an important element of workplace safety for preventing occupationally acquired HIV infection (Table 73.8).

Zidovudine (ZDV) postexposure prophylaxis (PEP) appears to reduce the risk for HIV transmission after occupational exposure to HIV-infected blood. ZDV PEP was associated with a decrease of approximately 79% in the risk for HIV seroconversion after percutaneous exposure to HIV-infected blood in a case-control study among healthcare workers.

The average risk for HIV infection from all types of reported percutaneous exposures to HIV-infected blood is 0.3%. In the case-control study, risk was increased for exposures involving (1) a deep injury to the healthcare worker, (2) visible blood on the device causing the injury, (3) a device previously placed in the source patient's vein or artery (e.g. a needle used for phlebotomy), or (4) a source-patient who died as a result of acquired immunodeficiency syndrome (AIDS) within 60 days post-exposure (and therefore was presumed to have a high titer of HIV). The risks after mucous membrane and skin exposures to HIV-infected blood (on average, approximately 0.1% and<0.1%, respectively) probably also depend on volume of blood and titer of HIV. The risk is probably higher for skin contact that is prolonged, involves an area that is extensive or in which skin integrity is visibly compromised, and/or involves a higher HIV titer.

Recommendations

The following CDC recommendations are provisional because they are based on limited data regarding efficacy and toxicity of PEP and risk for HIV infection after different types of exposure. Because most occupational exposures to HIV do not result in infection transmission, potential toxicity must be carefully considered when prescribing PEP. When possible, these recommendations should be implemented in consultation with persons having expertise in antiretroviral therapy and HIV transmission. Changes in drug regimens may be appropriate, based on factors such as the probable antiretroviral drug resistance profile of HIV from the source patient; local availability of drugs; and medical conditions, concurrent drug therapy, and drug toxicity in the exposed worker. These recommendations were not developed to address non-occupational (e.g. sexual) exposures.

(1) Chemoprophylaxis should be recommended to exposed workers after occupational exposures associated with the highest risk for HIV transmission. For exposures with a lower, but non-negligible risk, PEP should be offered, balancing the lower risk against the use of drugs having uncertain

TABLE 73.8 1996 provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV, by type of exposure and source material

Type of exposure	***Source material***[a]	***Antiretroviral prophylaxis***[b]	***Antiretroviral regimen***[c]
Percutaneous	Blood[d]		
	Highest risk	Recommend	ZDV plus 3TC plus IDV
	Increased risk	Recommend	ZDVplus3TC±IDV[e]
	No increased risk	Offer	ZDV plus 3TC
	Fluid containing visible blood, other potentially infectious fluid[f], or tissue	Offer	ZDV plus 3TC
	Other body fluid (e.g. urine)	Not offer	
Mucous membrane	Blood	Offer	ZDVplus3TC±IDV[e]
	Fluid containing visible blood, other potentially infectious fluid[f], or tissue	Offer	ZDV±3TC
	Other body fluid (e.g. urine)	Not offer	
Skin, increased risk[g]	Blood	Offer	ZDVplus3TC±IDV[e]

	Fluid containing visible blood, other potentially infectious fluid[f] or tissue	Offer	ZDV±3TC
	Other body fluid (e.g. urine)	Not offer	

[a]Any exposure to concentrated HIV (e.g. in a research laboratory or production facility) is treated as percutaneous exposure to blood with highest risk.
[b]Recommend: Postexposure prophylaxis (PEP) should be recommended to the exposed worker with counseling (see text). Offer: PEP should be offered to the exposed worker with counseling (see text). Not offer: PEP should not be offered because these are not occupational exposures to HIV.
[c]Regimens: zidovudine (ZDV), 200 mg tid; lamivudine (3TC), 150 mg bid; indinavir (IDV), 800 mg tid (if IDV is not available, saquinavir may be used, 600 mg tid). Prophylaxis is given for 4 weeks. For full prescribing information, see package inserts.
[d]Highest risk: BOTH larger volume of blood (e.g. deep injury with large diameter hollow needle previously in source patient's vein or artery, especially involving an injection of source-patient's blood) AND blood containing a high titer of HIV (e.g. source with acute retroviral illness or end-stage AIDS viral load measurement may be considered, but its use in relation to PEP has not been evaluated. Increased risk: EITHER exposure to larger volume of blood OR blood with a high titer of HIV. No increased risk: NEITHER exposure to larger volume of blood NOR blood with a high titer of HIV (e.g. solid suture needle injury from source patient with asymptomatic HIV infection).
[e]Possible toxicity of additional drug may not be warranted (see text).
[f]Includes semen; vaginal secretions; cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids.
[g]For skin, risk is increased for exposures involving a high titer of HIV, prolonged contact, an extensive area, or an area in which skin integrity is visibly compromised. For skin exposures without increased risk,the risk for drug toxicity outweighs the benefit of PEP.

efficacy and toxicity. For exposures with negligible risk, PEP is not justified. Exposed workers should be informed that (a) knowledge about the efficacy and toxicity of PEP is limited; (b) for agents other than ZDV, data are limited regarding toxicity in persons without HIV infection or who are pregnant; and (c) any or all drugs for PEP may be declined by the exposed worker.

(2) At present, ZDV should be considered for all PEP regimens because ZDV is the only agent for which data support the efficacy of PEP in the clinical setting. Lamivudin (3TC) should usually be added to ZDV for increased antiretroviral activity and activity against many ZDV-resistant strains. A protease inhibitor (preferably indinavir (IDV) because of the characteristics summarized in this report) should be added for exposures with the highest risk for HIV transmission (Table 73.8). Adding a protease inhibitor also may be considered for lower risk exposures if ZDV-resistant strains are likely, although it is uncertain whether the potential additional toxicity of a third drug is justified for lower risk exposures. For HIV strains resistant to both ZDV and 3TC or resistant to a protease inhibitor, or if these drugs are contraindicated or poorly tolerated, the optimal PEP regimen is uncertain; expert consultation is advised.

(3) PEP should be initiated promptly, preferably within 1–2 hours postexposure. Although animal studies suggest that PEP probably is not effective when started later than 24–36 hours postexposure, the interval after which there is no benefit from PEP for humans is undefined. Initiating therapy after a longer interval (e.g. 1–2 weeks) may be considered for the highest risk exposures; even if infection is not prevented,

early treatment of acute HIV infection may be beneficial. The optimal duration of PEP is unknown; because 4 weeks of ZDV appeared protective, PEP should probably be administered for 4 weeks, if tolerated.

(4) If the source patient or the patient's HIV status is unknown, initiating PEP should be decided on a case-by-case basis, based on the exposure risk and likelihood of HIV infection in known or possible source patients. If additional information becomes available, decisions about PEP can be modified.

(5) Workers with occupational exposures to HIV should receive follow-up counseling and medical evaluation, including HIV-antibody tests at baseline and periodically for at least 6 months postexposure (e.g. 6 weeks, 12 weeks, and 6 months), and should observe precautions to prevent possible secondary transmission. If PEP is used, drug-toxicity monitoring should include a complete blood count and renal and hepatic chemical function tests at baseline and 2 weeks after starting PEP. If subjective or objective toxicity is noted, dose reduction or drug substitution should be considered with expert consultation, and further diagnostic studies may be indicated.

In currently recommended doses, ZDV PEP usually is tolerated well by health-care workers; short-term toxicity associated with higher doses primarily includes gastrointestinal symptoms, fatigue, and headache.

KNOWN OR PRESUMED EXPOSURE TO HBsAG

There are no prospective studies directly testing the efficacy of a combination of hepatitis B immune globulin (human) (HBIG) and RECOMBIVAX HB® in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, since most persons with such exposures (e.g. healthcare workers) are candidates for RECOMBIVAX HB® and since combined HBIG (human) plus vaccine is more efficacious than HBIG (human) alone in perinatal exposures, the following guidelines are recommended for persons who have been exposed to hepatitis B virus such as through:

(1) percutaneous (needle-stick), ocular, mucous membrane exposure to blood known or presumed to contain hepatitis B surface antigens (HBsAg);
(2) human bites by known or presumed HBsAg carriers, that penetrate the skin; or
(3) following intimate sexual contact with known or presumed HBsAg carriers.

Hepatitis B immune globulin (human) (0.06 ml/kg) should be given intramuscularly as soon as possible after exposure and within 24 hours if possible. RECOM-BIVAX HB® should be given intramuscularly at a separate site within 7 days of exposure and second and third doses given one and six months, respectively, after the first dose.

RECOMBIVAX HB® is for intramuscular injection. The deltoid muscle is the preferred site for intramuscular injection in adults. Data suggests that injections given in the buttocks frequently are given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than was expected. The anterolateral thigh is the recommended site for intramuscular injection in infants and young children.

Recommendations for hospital employees pricked by needles

I. For an employee who is stuck by a needle from a known hepatitis B (HBsAg+) patient:

(1) Draw a sample of the employee's blood for determinations of SGOT, SGPT, HBsAg and anti-HBs.
(2) If the employee is:

(a) negative for both HBsAg and anti-HBs, give HBIG 0.06 ml/kg within 7 days after exposure and again 28–30 days after exposure.
(b) HBsAg-positive or has anti-HBs, there is no need to administer hyperimmune globulin.

(3) Draw follow-up blood samples at 2 and 6 months after exposure for retesting of SGOT, SGPT, HbsAg, and anti-HBs.
(4) No tetanus toxoid is necessary.

II. For an employee who is stuck by a needle from a patient who does not have hepatitis and is known to be HBsAg-negative:

(1) Reconfirm the patient's HBsAg status.
(2) If the patient is:

(a) reconfirmed HBsAg-negative, no treatment is necessary for the employee.
(b) HBsAg-positive, follow procedure I.

III. For an employee who is stuck by a needle from a patient with hepatitis or other active liver disease whose HBsAg status is unknown or is known to be negative:

(1) If the patient is HBsAg-negative:

(a) Reconfirm the patient's HBsAg status. If negative, continue as listed below in b, c, and d. If the patient is HBsAg-positive, follow procedure I.
(b) Draw blood from the employee for baseline SGPT, SGOT, and HBsAg values.
(c) Give standard immune serum globulin (ISG) 0.02 ml/kg as soon as possible.
(d) Draw blood for follow-up SGOT, SGPT, and HBsAg testing at 4–6 weeks after exposure.

(2) If the patient's HBsAg status is unknown:

(a) Draw a sample of the patient's blood for HBsAg testing.
(b) If the patient's HBsAg is negative, follow procedure III, 1. If the patient's HBsAg is positive, follow procedure I.
(c) If the patient's HBsAg status cannot be determined, the employee must be treated as though patient is HBsAg-positive. Follow procedure I.

IV. For an employee who is stuck by a needle of unknown origin (e.g. a needle poking through a trash bag):

(1) Give tetanus toxoid if the employee has not had a tetanus booster within 5–10 years (because of possible soil contamination).
(2) Give HBIG as in procedure I. Although the chances are only about 1–2% that a needle of unknown origin came from a person who is HBsAg-positive, the risks associated with the administration of HBIG are so low that it seems prudent to treat the exposed individual. If the employee already has anti-HBs or HBsAg in the serum, treatment with hyperimmune globulin appears to be unnecessary. Hepatitis B immune globulin costs about $30/ml and its use should be restricted to situations in which it is indicated, as outlined here. The immune globulin should be administered within 7 days after exposure.

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Postoperative infections

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Pelvic operations are some of the most common procedures performed in the United States today. Surveys have demonstrated that hysterectomy is the second most frequently performed surgical procedure among reproductive aged women during the past decade. They often require incisions made through contaminated tissue, and thus are at high risk for developing postoperative infections.

The source, the species, and mechanisms whereby infection is established in pelvic surgery has been poorly understood in the past, as many principles are unique to gynecology and do not routinely follow abdominal surgery principles. However, recent research has demonstrated many of the mechanisms whereby infection is established, and with this knowledge, can be more effectively treated or prevented. Despite this knowledge, and because of the often contaminated nature of pelvic surgery (especially vaginal surgery), pelvic postoperative infections are still commonplace and must be addressed if serious postoperative morbidity and mortality are to be avoided. Ledger & Child, and others, have demonstrated that postoperative fever developed in 31% and 38% of abdominal and vaginal hysterectomies, respectively. As a corollary, antibiotics were administered in 45% and 54% of abdominal and vaginal hysterectomies, respectively. Infectious morbidity, defined as postoperative fever plus clinical indications of infection, have been reported following approximately 35% of vaginal and 20% of abdominal hysterectomies. There is infectious morbidity with not only hysterectomy, but also other pelvic surgery, and these will be discussed as well.

An understanding of etiology, microbiology, prophylaxis and treatment of pelvic infections is important to gynecologists. Cesarean section and other obstetric-related infections, while similar in microbiology, have very different etiologic and mechanical considerations and are discussed elsewhere. Also, non-pelvic sources of fever and infections such as pneumonia, urinary tract infections, etc. are similar to other surgical procedures, thus the main focus in this chapter will be on operative site (pelvic) infections.

ETIOLOGY

Hysterectomy

Hysterectomy, often thought of as one uniform procedure, is actually two or more very different procedures with respect to infectious morbidity. While abdominal and vaginal hysterectomies have very different routes of access, both eventually entail surgical entry into the vagina. A recently described and more common alternative is the supra-cervical

laparoscopic hysterectomy, which does not enter the vaginal cavity, and holds promise for decreasing infectious morbidity. However, this is a technically more difficult procedure, thus comparative studies with respect to operative morbidity will need to be conducted.

Abdominal hysterectomy, because of its initial entry through a hopefully uninflamed abdominal incision, is often misclassified as a 'clean' procedure. However, the ultimate incision into the vagina for removal of the cervix and uterine specimen generally results in gross contamination of the pelvic cavity by the vaginal flora. Thus, abdominal hysterectomy is now classified as 'clean'-'contaminated', and surgical surveys have demonstrated an infection rate of approximately 10%. However, 'clean'-'contaminated' procedures exclude cases with 'significant spillage', and the amount of contaminated fluid at the vaginal cuff is often-times significant in abdominal hysterectomies, and is persistent in vaginal hysterectomies, thereby, resulting in higher infection rates.

Such procedures, with gross spillage, or those performed in an inflamed area are classified 'contaminated', and typically have an infection rate of approximately 20%. Surgeries classified as 'dirty' procedures are those in which there is a perforated viscous, association with trauma, or purulent material was present in the operative field. 'Dirty' operations with pus present from a tuboovarian abscess or pyosalpinx, or re-operations for pelvic abscess, are examples most likely encountered by gynecologists, and the infection rates are 25% or higher, despite antibiotic administration at surgery. Therefore, most abdominal hysterectomies are clean-contaminated or contaminated, and those infections such as pelvic inflammatory disease, abscess, etc, are classified as 'dirty'. In vaginal hysterectomy, the opposite of what occurs in abdominal hysterectomy takes place. Instead of a relatively clean procedure that concludes in a contaminated area (vagina), vaginal hysterectomies begin in a contaminated space, then progress into a sterile environment which is repeatedly contaminated over a period of one or more hours.

Following the removal of the uterus, with either hysterectomy route, there is great debate whether the surgeon should leave the vaginal cuff open, thus allowing drainage, or close the cuff to prevent further vaginal bacterial contamination. While there has been no definitive answer, it is best to look at the immediate outcomes versus late complications in order to decide if you wish to leave the cuff open. With a closed cuff, continuous drainage is prevented; however, potential bacterial growth media, (blood and serous fluid) can accumulate. Contamination from the vagina, if it has not occurred in significant amounts, may not infect such media, and serious infection, such as an abscess may be avoided. However, if significant contamination has occurred prior to closure, the developing infection is contained, drainage is prevented, and abscess or an infected hematoma may occur.

If the vaginal cuff is left open, drainage occurs continuously, and exposure of the operative site to persistent bacterial contamination is possible. However, drainage is one of the most important methods to treat or avoid infection, and if an abscess does develop, there is easy access for culture sample collection and further drainage. In a study, Martens *et al.*, utilized a hysterectomy surgical cuff stapler, which isolated, incised, and closed the vaginal cuff with dissolvable staples simultaneously. The theory behind this strategy was to reduce the contamination of the lower pelvic cavity, decrease necrotic tissue (the staples compress less than 0.5 cm of tissue) and decrease blood loss. The study demonstrated a statistically lower postoperative infection rate; however, adequate

exposure was necessary, and difficulty in drainage of abscesses (albeit at a significantly lower incidence) was noted.

Preventing the contamination of the surgical field is also one of the benefits of laparoscopically assisted supra-cervical hysterectomies (LASH), as the cervix is maintained and the vagina is not entered. Care must be taken to treat or cauterize the remaining endocervical canal without contaminating the pelvic cavity in the process.

Infection rates in laparoscopic supra-cervical hysterectomies do appear to be lower; however, large studies do not exist to compare other sources of morbidity. There exists the need to distinguish between laparoscopic supra-cervical hysterectomies (LASH), and laparoscopically-assisted vaginal hysterectomies (LAV), wherein the vagina is incised to permit removal of the specimen, thus contamination can occur at this time. The theoretical benefit, though, is that the entire procedure is not done through the contaminated vagina over one or more hours, and that the potential contamination occurs much later in the procedure. In the LASH procedure, the uterine specimen is morcellated and removed via the laparoscopic trocar, thus never requiring an incision directly into the vagina.

For all postoperative infections, there are three main factors: bacteria, growth media, and host immune responses that determine infection and its extent. While specific species will be discussed in the microbiology section, the origin and the quantity of bacteria are important and can vary. In abdominal hysterectomy, there are low numbers of organisms on the patient's skin in the abdominal area, and they are the source in the subsequent development of an abdominal wound infection. The rate of abdominal wound infections is generally low with a threshold set less than 5% by most quality assurance hospital committees. Certain factors are known to increase the rate in larger studies, including shaving of the skin the prior evening, operating in an infected area of the skin, and hypothermia. Additional factors, which may increase wound infection rates, are excessive use of electrocautery, excessive use of subcutaneous stitches (foreign body), and increased duration of surgery. Factors which have been demonstrated to help in decreasing wound infections include adequate skin decontamination/preparation, maintaining normal body temperature, wound lavage and in some studies, intravenous antibiotic prophylaxis.

The next factor relating to infectious morbidity in abdominal hysterectomies is related to the pelvic surgical procedure. Several studies have demonstrated that one of the strongest predictors of low infectious morbidity is good surgical technique. Good surgical technique decreases the second main factor in the development of all infections, that of growth media. Bacteria that gain access to the normally sterile pelvic cavity are maintained and proliferate in the presence of a nutritional environment suited to their growth requirements. Blood, serum, and necrotic tissue are excellent growth media for all bacteria. The presence or lack of oxygen can determine the species that predominate, either facultative anaerobic (often referred to as aerobes) or obligate anaerobes.

Poor surgical technique can result in increased bleeding. It can also result in excess necrotic tissue from large avascular pedicles, excessively electrocauterized tissue, or excessively large or frequent foreign body use (suture, graft, etc.) Even with excellent surgical technique, there will still be avascular pedicles present and serous and hematogenous accumulations will be present postoperatively. These sites for potential infections can become contaminated. Although occasionally it may be from bacteria

originating from the abdominal incision, it almost always originates from the cervico-vaginal flora that is encountered when the uterus is excised. Since the vagina is not sterile, all vaginal cuffs are therefore contaminated. Also, since all intra-abdominal and pelvic blood, and serous fluid will gravitate to the lowest part of the pelvis when the patient is upright and ambulatory, the vaginal cuff almost always has adequate nutrients to sustain bacterial growth. Healing of the vaginal cuff entails a proliferation of all of the inflammatory cells and fibroblasts, which in essence creates a cuff cellulitis. An inflammatory response is actually required for healing, and therefore is a normal response. However, persistent bacterial growth in this area or inadequate immunologic response will lead to worsening cellulitis, resulting in increasing serious infections such a pelvic cellulitis or pelvic phlegmon. Extension into thrombosed vessels may also lead to septic pelvic thrombophlebitis. The presence of infected fluid in an enclosed space often created by an extensive inflammatory response and fibroblast proliferation (adhesions) can result in an infected hematoma or vaginal cuff abscess.

The same process occurs in vaginal hysterectomy. However, since the bacterial contamination starts early in the procedure and is often of greater magnitude, a higher incidence of postoperative infection is often seen. Thus, the rate in premenopausal women is generally high enough to warrant routine surgical prophylaxis for vaginal hysterectomy.

Infections in other pelvic surgical procedures depend upon the source of bacterial contamination and the extent and location of the surgical site.

Ovarian surgery

The ovary is a site for serious infections under certain conditions. The ovaries do not generally become infected if they are left intact following a hysterectomy or other pelvic procedure. However, if the capsule is violated, as with incision or drainage of a cyst or biopsy, any bacteria present may result in an infection. Once the ovary is infected, it is not uncommon for it to progress to abscess formation, causing the need for re-operation and removal. Even pelvic procedures, which do not affect the ovary itself, may result in serious ovarian infection, such as was demonstrated over a half-century ago with the development of serious ovarian abscesses following colpotomy tubal ligations. It was determined that ovulation and the subsequent rupture of the ovarian capsule allowed the entrance of bacteria into the ovarian tissue, especially with vaginal surgical procedures.

Thus, it is important to attempt to schedule elective surgical procedures wherein the ovaries will be spared, if possible, into the late luteal phase in ovulating women. It is also important to avoid penetrating the capsule unless absolutely necessary. Therefore, the practice of needle drainage of small ovarian cysts is not recommended and should be avoided if possible.

Myomectomy

Myomectomy is another pelvic procedure which has a high incidence rate, and seriousness of infection. This is a result of the extensive blood supply of the myoma, and the difficulty in achieving hemostasis. The combination of extensive use of foreign body (suture), and necrosis to achieve hemostasis, and the presence of fibroid and serous fluid

leads to a fertile area for bacterial contamination to flourish. Fortunately, since the vagina is not entered such as with a hysterectomy, exogenous bacteria from the abdominal incision are few in number and usually do not cause infection. However, if the endometrial cavity is penetrated with the removal of the myoma, contamination from crevice-vaginal flora that has entered the endometrial cavity can occur. McGregor and others have demonstrated that the premenopausal endometrial cavity is not sterile, and routinely has fluid and bacteria circulating from the lower to the upper genital tract. However, without a focus for bacterial entry into the uterine tissue, infection is rare except in patients with sexually transmitted diseases present in the cervix, resulting in upper genital tract infections, routinely called salpingitis or pelvic inflammatory disease. However, with myomectomy and entry into the endometrial cavity, bacteria may have a site to enter and proliferate.

Laparoscopy

Most pelvic operative laparoscopic procedures may leave behind blood and necrotic tissue, but fortunately bacterial contamination is usually minimal. However, because of the increased difficulty of these procedures, and the limited access for evaluation of the pelvis prior to closing, perforation of a viscus may occur. The bacterial contamination resulting from these procedures are often devastating, as the patient often is an outpatient, and early signs and symptoms of infection are missed with the patient at home. Once re-hospitalized and discovered, extensive infection and abscess formation is often present, requiring extensive debridement, drainage, and repair.

Hysteroscopy

Infections after hysteroscopy are less frequent, due to the relatively minimal tissue damage, and with a patent endocervical canal drainage is naturally present. However, uterine ablation can leave an extensive necrotic area, which can easily get infected if bacteria are present, or perforation into the pelvic cavity can occur incidentally, or with large myoma or septum removal. Bacteria present in the hysteroscopic distension fluid or postoperatively from the crevicevaginal flora can cause uterine or pelvic infection, and need to be considered in a patient with fever and/or pelvic pain. However, infection from transcervical fluid administration is rare with hysteroscopy, but has been reported with hysterosalpingograms, as the goal of the procedure is to get past the uterine cavity also.

Dilatation and curettage (D & C)

While classified as a relatively minor procedure, infections following D & C are not uncommon. These infections are due to the transvaginal nature of the procedures resulting in contamination by cervicovaginal flora of the endometrial cavity (now disrupted by curettage), and an increased likelihood of tissue invasion. The resulting infection is an endometritis, which may spread if not recognized early or progress to parametritis or abscess if poor endocervical drainage allows build-up of blood and necrotic debris to occur.

Tubal ligation

As mentioned earlier, serious infection can occur with poorly timed colpotomy ligation procedures; however, the rate of infection from the abdominal approach is generally low. Laparoscopic site infections are more common than extensive pelvic procedures, but can occur and are often associated with a hematoma that may occur at the ligation site or within the broad ligament.

MICROBIOLOGY

Just as the source of the bacteria in gynecologic infections is different than other procedures, the specific species are also different. Therefore, an understanding of the organisms responsible for postoperative infections is important, so that the most appropriate therapy can be utilized. Again, for most cases, of postoperative pelvic infections originate from the cervico-vaginal flora, and are most often polymicrobial in nature. Numerous studies have demonstrated the wide variety of pathogens recovered from patients diagnosed with postoperative pelvic infections. Many of these studies have been performed during trials of antibiotics utilized to gain FDA approval for an indication for treatment of gynecologic infections. Table 74.1 is a compilation of three such studies, and demonstrates the presence of Gram-positive cocci, then anaerobes then Gram-negative rods, in that order of frequency. However, many of these studies included patients who received surgical antibiotic prophylaxis; Ohm and Galask studied the microbiology of 100 patients prior to hysterectomy, and found the most frequent organisms present were Gram-positive cocci, Gram-negative rods, then anaerobes in that order. The discrepancy between the preoperative cultures and the postoperative cultures represents the effect that prophylactic antibiotics has on the patient's endogenous flora. Several studies, including Faro and Martens, in a prospective, randomized analysis of over 1000 patients receiving single or multiple dose prophylaxis, demonstrated that even single dose antimicrobial prophylaxis increased the number of Gram-positive (specifically enterococci) cocci, and decreased the Gram-negative rods present postoperatively.

The recovery of a variety of organisms in infected patients mimics the animal studies performed first by Gorbach, and then by Martens and colleagues a decade later. In these studies, inoculums of aerobes, with or without anaerobes, were implanted into rat abdomens and pelvises to ascertain the natural history of abdominal and pelvic infections. Implanted aerobic organisms routinely resulted in severe peritonitis, and a significant increase in abscess development followed in those patients that also had anaerobes implanted. Gorbach's model utilized intra-abdominal pathogens, and Martens' experiments utilized pathogens isolated from female pelvic infections.

This 'anaerobic progression' model whether with pathogens such as the enteric aerobes and *Bacteroides fragilis* in Gorbach's model, or a variety of enterococci or Gram-negative rods plus *Prevotella bivia* and the anaerobic streptococci in the Martens' model, support the theory of an early aerobic inflammatory response altering the environment through a change in the pH, redox potential, and reduced oxygenation to create a favorable environment for obligate and facultative anaerobes. This explains in part why prophylactic antibiotics that do not have excellent anaerobic activity still

provide adequate prophylaxis, as they interrupt the anaerobic progression at an early stage. However, when infection is established, several studies have demonstrated the importance of using antibiotics that have adequate anaerobic activity.

Fortunately few studies in immunocompetent patients demonstrate the presence of multiply resistant Gram-negatives such as those with extended spectrum beta-lactamase enzymes *(Pseudomonas, Serratia, Halico influenzae)* in non-oncology gynecology patients. They can be present in patients who have been on long-term antibiotic treatment, especially with cephalosporins, often for urinary tract or skin infections. The most frequently isolated of the multiply-resistant *Enterobacteriaceae* is *Halico Enterobacter cloacae,* which is becoming a much more frequent isolate, often after short course prophylactic regimens with cephazolin or cefoxitin. The enterococci also are becoming much more prevalent, due to the extensive and almost exclusive cephalosporin use for prophylaxis. In most studies, enterococci are recovered in well over 50–60% of patients after cephalosporin prophylaxis use. While treatment of enterococci may not be essential in all patients when multiple organisms are recovered, it should still be respected as a pathogen, and definitely covered if the patient does not respond to adequate broad spectrum empiric coverage that excludes enterococci activity, such as with clindamycin-gentamicin, cefoxitin and all other cephalosporins, and even the penicillin-beta-lactamase combination, ticarcillin-clavulanate. Adding ampicillin or switching to the betalactamase combinations of ampicillin-sulbactam or piperacillin-tazobactam provides excellent enterococci coverage.

The anaerobe most studied in intra-abdominal infections *Bacteroides fragilis* is a bowel pathogen; however it is not the most frequent anaerobe found in pelvic infections. The anaerobic streptococci and peptococci are the most frequent Gram-positive anaerobes, and the *P. bivia* and *P. melaninogenicus* are the most frequent Gram-negative anaerobes isolated. The *Prevotella* species were previously classified as *Bacteroides* species, however their growth requirements and susceptibility profiles were sufficiently different to justify reclassification. The anaerobic streptococci are highly susceptible to most broad-spectrum cephalosporins and penicillins. However, the Gram-negative anaerobes often require specific anaerobic therapy with the penicillin-beta-lactamase combinations, the carbapenems, metronidazole, and then clindamycin, in order of activity.

PROPHYLAXIS

While much of this discussion will be centered around intravenous antibiotic prophylaxis, other routes or methods have been demonstrated to decrease the incidence of postoperative infection. Swartz and Tanaree in 1976 demonstrated that T-tube suction drainage of the vaginal cuff was as effective as prophylactic antibiotics. Also, endocervical penicillin antibiotics, vaginal metronidazole and oral trovofloxacin have demonstrated statistically significant efficacy in reducing post-hysterectomy infections. However, the most widely utilized prophylactic regimen is intravenous antibiotic administration immediately prior to the gynecologic procedure. Numerous studies have demonstrated the efficacy of dozens of antibiotic regimens. Rather than listing the myriad

of options, it is better to review the basic principle of antibiotic prophylaxis initially proposed by Ledger, and then modified by Johnson and colleagues.

The operation should have a significant risk for operative site infection. While early studies and infectious disease guidelines limited prophylactic antibiotics to premenopausal women undergoing vaginal hysterectomy only, recent large meta-analyses have found that antibiotics benefit both abdominal and vaginal hysterectomy procedures. Also, while the postmenopausal vagina has been found to have a decreased quantity of vaginal flora, hormone therapy and urinary tract conditions have often shown that prophylactic antibiotic usage in this patient population may be helpful. Other procedures that may have significant contamination are administered antibiotic prophylaxis in selected areas. These include D & C, pregnancy termination, myomectomy with penetration into the endometrial cavity, hysterosalpingograms, colpotomy tubal ligations, and intrauterine device removals.

The operation should be accompanied by endogenous bacterial contamination. Any procedure whereby the vagina is entered, such as hysterectomy, has a high-risk of contamination and should receive prophylaxis. However, abdominal procedures that do not enter the genitourinary tract are usually at low-risk of contamination or infection (such as mini-laparotomy tubal ligations, endometriosis ablation or resection, and most laparoscopic procedures), and do not require prophylaxis for this reason.

The prophylactic antibiotic should have laboratory and clinical evidence of effectiveness against some of the contaminating organisms. Most agents have activity against some if not many of the polymicrobial endogenous female flora, and thus have usually shown effectiveness in studies of surgical prophylaxis versus placebo. However, some agents have demonstrated statistical superiority over other antimicrobial agents. In 1995, Heinsell and associates demonstrated the inferiority of cephazolin when compared to cefotetan in hysterectomy prophylaxis.

The prophylactic antibiotic should be present in the wound, preferably before incision, and should reach a therapeutic concentration in operative site tissues. Fortunately most antibiotics are well distributed in the body, and if administered in a timely manner reach therapeutic levels. However, some antibiotics do not accumulate in pelvic tissues, such as nitrofurantoin, and thus would not be effective. Also, errors in the time of administration also decrease the antibiotic efficacy. Several studies have demonstrated that up to 50% of cases are subject to administration of the dose too early prior to surgery, due to delays in transportation or anesthesia, resulting in and declining levels being present in the tissue at time of incision. Administering the antibiotic once the patient is in the operating room avoids this problem of declining tissue levels, but increases the risk of late administering resulting in the incision being made before the antibiotic can reach therapeutic levels or is given at all. Several antibiotics have long half-lives and thus delayed time to peak levels, and thereby would also be poor candidates for prophylaxis. An example is azithromycin, which has a much longer time required to reach peak levels, and thus would be a poor prophylactic agent. Oral agents used for bowel decontamination and oral vancomycin also are not absorbed significantly enough to be helpful in prophylaxis.

A short course of prophylactic antibiotics should be used. Fortunately, the excessive use of multiple days (sometimes up to several days) of ‘prophylaxis’ administration is found with less frequency. In fact, any prophylaxis with dosage lasting more than 24 hours is technically ‘treatment’ and not prophylaxis. Also, use of repeated smaller doses

of prophylaxis makes little sense, as why would one expect a sub-therapeutic dose that failed to kill a significant number of bacteria initially be of any success at the same sub-therapeutic dose several hours later when the bacterial numbers are growing? Most studies have demonstrated that a single dose of antimicrobial prophylaxis is as effective as multiple (usually three) doses. While efficacy of the first dose of prophylaxis in lengthy hysterectomy procedures was found to be no more effective than placebo after several hours of surgery, this study by Shapiro and colleagues has been misquoted to justify administering a second dose if the operating time is greater than 3 hours. This was not studied by these investigators, and while theoretically it may seem reasonable, it is equally plausible that prophylaxis has failed and that treatment, and not repeated prophylaxis with the same agent is required. Therefore, single agent, single dose prophylaxis is generally recommended.

Therapeutic agents should be reserved for therapy unless demonstrated superior to other agents. Antibiotic prophylaxis is not foolproof and therefore therapeutic agents to which the patient's pathogenic flora has not been exposed to recently would give the patient the best chance at recovery. Few studies have demonstrated superiority, with the exception of the recently discussed Heinsell study on cefotetan use for hysterectomy prophylaxis. Faro and Martens also demonstrated cefotetan and piperacillin's superiority over several other prophylactic regimens in Cesarean section; however, use of these agents for prophylaxis, and then treatment of subsequent antibiotics failures, would not be recommended.

Benefits of antibiotic prophylaxis should outweigh the risks. While in most instances the risk is minimal, the main determinant of choosing a specific antibiotic resides with its efficacy. This efficacy is determined by the factors discussed previously, activity versus pelvic pathogens, tissue penetration, etc. However, there are certain instances whereby excessive risk for prophylaxis may be present, such as a patient with multiple antibiotic allergies, or significant side-effects, such as rash from sulfa drugs or gentamicin use in a patient with renal failure.

DIAGNOSIS

Once a prophylaxis fails or was not utilized, a postoperative infection must be diagnosed properly before treatment can be chosen. The most commonly used sign utilized by almost all physicians is to check for temperature elevations postoperatively. Postoperative white blood cell (WBC) counts are also often checked. However, they are often mildly elevated, and are rarely acted upon independent of fever. Postoperative pain is an expected sign and even if present in heightened fashion, is not indicative only of infection. Low-grade fevers between 37.5ºC and 40ºC are often present early in the postoperative course. Following extensive pelvic surgery, such as with hysterectomy, it is usually the result of the inflammatory healing process and vaginal cuff contamination that invariably occurs in all such procedures. This is described by Hemsell and others as 'cuff cellulitis', and when it progresses, rarely cause significant fever or clinical symptoms to warrant antibiotic therapy. In cuff cellulitis, the vaginal cuff is erythematous, and mildly edematous, may ooze a slightly purulent or serosanguinous discharge, and will be mildly to moderately tender. However, these signs and symptoms should be improving each day,

and should begin to resolve in two to five days. If cuff cellulitis progresses to a pelvic cellulitis, the extensive inflammatory response will often manifest itself with a fever of at least 38ºC and an increasing WBC count. Abdominal symptoms of increasing tenderness to deep palpation, and pelvic examination will reveal increased induration. An extensive 'balsa-wood' type consistency of the entire vaginal cuff area is consistent with pelvic phlegm or phlegmon, and a tender, fluctuant mass at the vaginal apex is consistent with a hematoma or abscess. Drainage of pus with palpation or probing of the cuff is synonymous with a cuff abscess and requires immediate drainage. Ultrasound or CT evaluation is often performed, but not immediately necessary unless ruptured pelvic abscess or multiple abscesses are suspected, or the patient fails initial drainage and treatment of the cuff mass.

While (a temperature equal to or greater than 38ºC) is the most sensitive and reliable sign of infection, its absence does not rule out infection, as antipyretics are often used or intermittent readings miss the fever's peak. It is recommended that meperidine or morphine be utilized in the first 24 to 48 hours until the presence or absence of fever can be ascertained. Low-grade fevers (<38ºC) do not immediately need to be treated, but should be investigated (i.e. antipyretics stopped, baseline laboratory values obtained, and a physical examination including evaluation of pulmonary status, urinary tract, wound, abdominal exam, pelvic exam, and bloody or vaginal discharges performed. Statistically, almost all temperature elevations greater than or equal to 38ºC (100.4ºF) represent an infection. If untreated, most will still resolve spontaneously, but a quicker return to normal and a decrease in abdominal and pelvic pain will be accomplished if the patient gets worked up for a pelvic infection and treatment is initiated if confirmed. Atelectasis, urinary tract infection, or wound infection rarely cause temperatures greater than 38ºC in the first 48 hours. Aspiration pneumonia, pyelonephritis, or bowel perforation will cause a rapid and early rise in temperature, and need to be evaluated immediately. Patients with an early low-grade fever that begins to have a spiking appearance, despite an improvement in the patient's clinical exam, should alert the physician to the possibility of septic pelvic thrombophlebitis. Cultures are often difficult to obtain, but can be helpful if the patient's condition is deteriorating rapidly. Blood and urine cultures for fevers higher than 38.5ºC can be obtained, and a transvaginal culture can be obtained if a mass is present. If the cuff has been closed, needle aspiration of the mass after the vaginal cuff is cleaned with betadine is acceptable to get the culture at the time of drainage. If the cuff has been left open, a culture swab, needle, aspirate, or replacement of drain can be utilized to get a sample. A stat Gram-stain should be obtained, as culture results will not be available for a few days. Culture results can help direct antimicrobial therapy, if the initial empiric choices fail or additional undrained abscesses are suspected.

Infection in pelvic surgery, other than hysterectomy is more difficult to diagnose. Endometrial sampling by aspirate can be performed in patients with a transmural myomectomy or dilatation and curettage. However, suspected ovarian masses will need radiologic evaluation of abscesses development, if the physical exam is suggestive of an intra-abdominal process and the ovarian capsule was violated, making it more likely that contamination of the ovary had occurred.

TREATMENT

Once a pelvic infection has been diagnosed, antimicrobial therapy should be initiated. This initial therapy is invariably empiric in nature, and must cover a variety of organisms, as these infections are frequently polymicrobial. However, several factors can help direct therapeutic choices. Prophylaxis with a cephalosporin should lead the physician to consider the enterococci as a possible pathogen, and a penicillin-based broad-spectrum agent such as piperacillin-tazobactam, or ampicillin-sulbactam should be considered. However, the traditional 'gold standard' of clindamycin and gentamicin has not been proven in comparative trials to be either superior or inferior. However, the administering of two separate agents and the potential toxicity of gentamicin, with its suggested peak and trough levels may not result in significant cost savings for these relatively inexpensive drugs. While costs can be saved by ordering the admixing of these drugs, and using once daily large dose gentamicin, ampicillin is often added, again raising costs and inconvenience.

The carbapenems, imipenem and meropenem, a have been well studied for the treatment of pelvic infections and demonstrate excellent results. Dosages for antimicrobial agents described are listed in Table 74.1. Ertapenem, a once a day intravenous carbapenem, has recently received approval for treatment of pelvic infections. However, usage has been limited and costs may be high. Prohibitive when compared to the more widely used carbapenems, the broad-spectrum cephalosporin agents with demonstrated efficacy include cefoxitin, cefotetan, ceftizoxime, and cefotaxime. Anaerobic activity is adequate, and Gram-positive aerobic activity is excellent except for *Enterobacter* species increase with cefoxitin, and poor *Pseudomonas* species coverage with most of these agents. Ceftriaxone has poor anaerobic activity and would be a poor choice for polymicrobial coverage of a soft-tissue pelvic infection.

A frequent concern from other specialties regarding the development of resistance with the use of the newer broad-spectrum agents such as piperacillin-tazobactam or imipenem is not valid, as the alternative clindamycin-gentamicin or the cephalomyins such as cefoxitin or cefotetan have been found to cause increases in *Clostridium difficile* and multiply-resistant enterococci. Also, use of antimicrobial therapy in gynecology is generally of short duration and usually does not require oral antimicrobial therapy after discharge from the hospital. While on antimicrobial therapy, patients should be monitored for improvement with repeat WBC counts to demonstrate systemic improvement. C-reactive protein (not the high sensitivity test used for cardiac risk evaluation) has been demonstrated

Table 74.1 Recommended parenteral therapy of pelvic infections

	Dose/interval
Piperacillin-tazobactam (Zosyn)	3.75 g q 6 h or 4.5 g q 8 h
1 imipenem-cilastatin (Primaxin)	500 mg q 6–8 h
Ampicillin-sulbactam (Unasyn)	3 g q 6 h
Ticarcillin-clavulanate (Timentin)	3.1 g q 6 h
Levofloxacin (Levaquin)	500 mg q 24 h
Clindamycin-gentamicin (Cleocin)	800 mg q 8 h Plus 5–7 mg/kg q 24 h
Meropenem (Merem)	1 g q 24 h
Cefoxitin (Mefoxin)	2 g q 6 h
Clindamycin-Aztreonam (Cleocin-Azactam)	800 mg q 8 h admix 500 mg q 8 h

in studies to correlate with improvement. It is important to make certain the patient is afebrile for at least 24 to 48 hours. Most antibiotics will cause the reduction of fever, which should occur within 48 hours. If the patient is not afebrile in that time period, a therapeutic failure needs to be considered. There are few, if any, reasons why therapy should be continued if a patient remains febrile after 2–3 days. Causes for failure are varied, but include uncovered bacterial species, abscess, septic pelvic thrombophlebitis or the development or progression of another infection at a distant site. As most patients will not have had a culture of the operative site, and antibiotics were begun empirically, the weaknesses of the treatment antimicrobial should be covered. While there are not hard, fast rules clindamycin-gentamicin patients should have ampicillin added to cover enterococci. Cefoxitin or other cephalosporin patients should be switched to cover the enterococci and resistant Gram-negative bacteria; piperacillin-tazobactam has the best coverage as a secondary agent. Imipenem and meropenem have equally excellent activities; however, if they have a slight weakness, it is in the area of enterococci. Ticarcillin-clavulanate patients often require a switch to piperacillin-tazobactam or ampicillin-sulbactam to cover enterococci. Ampicillin-sulbactam has some Gram-negative weaknesses, and an aminoglycoside or aztreonam provides excellent coverage. If the most active agents, piperacillin-tazobactam or the carbapenems, are not successful as empiric agents; equal consideration should be given to finding another cause for the fever as to expansion of the antimicrobial coverage. Piperacillin-tazobactam has a small number of resistant Gram-negative species that would be covered with an

aminoglycoside, and meropenam or imipenem misses few, but some enterococci. However, the activity is so broad that work-up of an undrained collection (abscess or infected hematoma) should be initiated. Pelvic examination with or without radiologic evaluation is strongly suggested. Also, if the patient is clinically improving, but has repeated temperature spikes, consideration of septic pelvic thrombophlebitis should be entertained as described earlier.

The broad-spectrum quinolones are also excellent agents, but have had limited use in pelvic infections outside of pelvic inflammatory disease (PID). However, many of the organisms are similar, especially in cases of non-gonococcal and non-chlamydial PID, and response should be similar. Martens and colleagues specifically studied pelvic pathogens activity with various quinolones and found that trovofloxacin has excellent female pelvic pathogen coverage (although it is essentially off the market) as does ofloxacin. Levofloxacin should have similar activity, and is often used interchangeably with ofloxacin. Ciprofloxacin, while an excellent antibiotic-pseudomonal agent, has poor pelvic anaerobic activity and is not recommended. Newer quinolones, such as moxifloxacin, have not been tested extensively against pelvic pathogens, but susceptibility data indicate that they would have equally inferior coverage for pelvic infections, similar to ciprofloxacin.

Also, of all the treatments mentioned, ofloxacin, (and probably levofloxacin) do not kill vaginal lactobacilli, and should have less effect on the promotion of vaginal flora shifts or fungal superinfections. With regard to failure of empiric therapy, a thorough work-up for undrained collections or other sites of infections should be initiated at any time after initial empiric therapy, or after secondary treatment coverage is not successful. Detection of an undrained and suspected infected hematoma or radiologic evidence of an abscess necessitates immediate drainage. Percutaneous drainage, guided by ultrasound or CT, has also been demonstrated to be successful. However, if a ruptured abscess is suspected or the patient is septic and unstable, exploration is imperative. If the patient appears to have been recovering from treatment of the pelvic infection, but then becomes febrile again, and it is at least 3–4 days postoperative, the abdominal wound should be inspected and opened if an abscess or seroma is suspected. Any blackened or necrotic area, or rapidly progressing erythema, should be taken back to the operating room and debrided immediately for fear of the development of necrotizing fasciitis. Other sites to inspect in response to persistent or recurrent fevers such as the intravenous site, pulmonary or urinary sources should be evaluated and treated if found. However, atelectasis or cystitis is not a source of persistent fever, and the search for the actual cause of the fever should continue. Lastly, in a small percentage of patients who receive pelvic instillation of hyaluronate-ferrous adhesion gel (Integel), indicated for adhesion prevention, fever in a small number of patients has been known to occur. If the WBC count is not elevated and evidence of a bowel perforation is absent, the fever often resolves spontaneously in these cases.

CONCLUSION

Gynecologic procedures are some of the most common operations in the United States today. Their clean-contaminated or contaminated classification means a significant

number of postoperative infections can occur. Proper surgical technique and appropriate use of prophylactic antibiotics will help to significantly decrease the incidence of postoperative infections, but many will still occur. The most important factor in successful treatment, however, is not antimicrobial choice, but early diagnosis and initiation of appropriate antimicrobial therapy. Delay in diagnosis, often a result of not recognizing or respecting the signs and symptoms of infection, such as fever, makes successful treatment increasingly difficult. Also, a complete, thorough history and physical examination is imperative to make the correct diagnosis once fever is present and infection is suspected.

A rapid response to therapy should occur, and again, delay in reacting to persistent fever and to the re-examination of the patient will eventually result in serious consequences. Thus a respect for fevers and infections will usually allow you to rapidly cure the patient and give her the favorable outcome for which she came to undertake surgery initially.

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75
Acute salpingitis

Traditionally, the term pelvic inflammatory disease (PID) has been applied to the infectious inflammatory process involving the uterus and/or fallopian tubes. Its broad connotations aggregated various processes of diverging origins. While a convenient categorical term, it does little for the conceptualization of the process functioning within a given patient.

> *'The term PID does not specify the anatomic distribution of the infectious process or the prognostic consequences for the woman afflicted. Is it not time to replace the diagnosis "pelvic inflammatory disease" with more precise terminology such as endometritis, salpingitis, or pelvic peritonitis.'*
>
> **Lars Westrom, MD DMS**
> *J Am Med Assoc* 1991; 866:2612

Certain disease processes require individualization. Early in the course of genital tuberculosis or coccidioidomycosis, salpingitis can occur independently of serosal extension or endometrial spread. Similarly, the group A beta-hemolytic streptococci are more prone to produce combined endometritis and peritonitis rather than endometritis, salpingitis, and peritonitis. The combination of endometritis and peritonitis in the immediate postpartum period differs significantly, bacteriologically and mechanistically, from endometritis-salpingitis with or without peritonitis observed in a non-gravida.

The Center for Disease Control's definition of PID has been a significant factor in the failure to achieve precise diagnostic and therapeutic end-points. According to the 1997 MMWR, 'PID comprises a spectrum of inflammatory disorders of the female genital tract, including any combination of endometritis, salpingitis, tuboovarian abscesses, and pelvic peritonitis. Sexually transmitted organisms, especially *Neisseria gonorrhoeae,* and *Chlamydia trachomatis* complicate most cases. However microorganisms that can be part of the vaginal flora, e.g. anaerobes, *Haemophilus vaginalis, H. influenzae,* enteric Gram-negative rods and *Streptococcus agalaxtie* can cause PID. In addition, *Mycoplasma hominis, Ureplasma urealyticum* might be etiological agents.'

This definition has come under severe criticism by the International Infectious Disease Society for Obstetrics and Gynecology (I-IDSOG). The Society reiterated advocacy for terminating the term PID previously advanced by other groups with in the discipline of Obstetrics and Gynecology. Recognizing how ingrained PID is in the world literature, it was proposed that if the term PID were to be used instead of upper female genital tract infection, it should be clarified as to anatomical sites of inflammation and etiological designation. The IIDSOG definition of PID is: 'Pelvic inflammatory disease is an inflammatory process of infectious etiology which shares a common epidemiological

profile (sexual risk factors), has at least uterine and fallopian tube sites of involvement and which may result in relatively comparable long term sequelae. Diseases due to bacteria not meeting these requirements will be designated upper female genital tract infection (UFGTI or UGTI) and specific or presumed etiology cited.'

The ensuing chapter will be restricted to those cases of acute salpingitis which are the consequence of venereal transmission.

PATHOGENESIS OF GONOCOCCAL SALPINGITIS

Initial gonococcal infection involves Skene's and Bartholin's glands and the endocervical and anorectal glandular sites. The predilection of *N. gonorrhoeae* to replicate successfully at these sites is in part a function of the alkaline milieu provided by the glandular secretions.

Table 75.1 The development of polymicrobial infections in patients with initial gonococcal infection*

Infection	Endocervix	Endometrium–fallopian tubes	Peritoneum–cul-de-sac
Gonococcal			
	(4+) *N. gonorrhoeae*	(2+) *N. gonorrhoeae*	
	(4+) *N. gonorrhoeae*	(2+) *N. gonorrhoeae* Class I aerobes	(1+) *N. gonorrhoeae*
	(3+) *N. gonorrhoeae*	(2+) *N. gonorrhoeae*	(1+) *N. gonorrhoeae* Class I anaerobes
	(2+) *N. gonorrhoeae*	(1+) *N. gonorrhoeae* Class II anaerobes	(Trace) *N. gonorrhoeae* Class I and II anaerobes
	(1+) *N. gonorrhoeae*	Polymicrobial mixed infection– Class II and III anaerobes	Polymicrobial mixed infection– Class II aerobes predominate
Non-gonococcal	Class I and III anaerobes	Class III anaerobes	Class II and III anaerobes

*Diagrammatic sequencing of the anaerobic progression as it applies to uncomplicated, untreated cases of gonococcal ESP. The flow, left to right, is the time representation proposed for the endocervix, endometrium-fallopian tubes, and peritoneum-cul-de-sac at given stages. (Monif GRG. Obstet Gynecol 55:1548, 1980)

Beyond organismal virulence factors such as pH, the elements selecting for disease, as opposed to infection, are not fully understood. The increased prevalence of salpingitis due to *N. gonorrhoeae* at the time of the menses has fostered the contention that the loss of mucosal integrity and the rich supply of subendolymphatics are important variables in transforming occult glandular infection into clinically recognized disease. Probably more important are the pH changes induced in the vagina as a consequence of the menses. The normal vaginal pH is approximately 4.2–4.9. The optimum pH for the replication of *N. gonorrhoeae* is 7.0 to 7.6. The pH of menstrual blood is usually 7.2. The occurrence of acute salpingitis beyond the time of the menses, its occurrence in patients several cycles after initial colonization, and its non-occurrence in other patients despite prolonged endocervical colonization, all focus on the complexity of the variables which combine to produce disease.

Gonococcal salpingitis is a consequence of the infectious agent with the appropriate genetic prerequisites obtaining access to the endometrial cavity by contiguous spread or insertion and the subsequent extension of the disease process to the fallopian tubes. With time, infection may reach the peritoneal cavity either through the fimbriated end of the fallopian tube or as a consequence of transmural penetration in the case of a ruptured tubo-ovarian complex.

When the disease process is initiated by *N. gonorrhoeae,* there is a progressive alteration in the microbiologic environment within the endometrial cavity (Table 75.1). This is accomplished by the postulated addition of substances which lower the local oxidationreduction potential, the removal of molecular oxygen, and the progressive reduction of local pH. The fall in pH influences the effectiveness of bacteriocins and bacteriocin-like products of bacteria which regulate strain dominance. This series of events is repeated within the fallopian tubes and cul-de-sac. With an open portal to the complex endocervical bacterial flora, the alterations induced by *N. gonorrhoeae* initiate the anaerobic progression. The bacteria thus recruited further transform the microbiologic environment. These bacteria are characterized by their progressive ability to replicate within a microbiologic environment characterized by a low redox potential and the relative absence of molecular oxygen. The farther removed the onset of disease is from the menses, the more likely the polymicrobial pattern is to be observed.

It is not *N. gonorrhoeae* but rather the superinfecting anaerobic bacteria which are responsible for basement membrane destruction and subsequent healing by fibrosis.

Pre-existing damage to the fallopian tube, if present, is thought to be associated with changes in tissue redox potential which favor earlier conversion to polymicrobial infection.

With time, *N. gonorrhoeae* is also eliminated at the endocervical site of infection through bacterial interference. In gonococcal salpingitis, the endocervix is both the first and the last site of bacterial replication. When the gonococcus is neither demonstrated on Gram-staining nor isolated from the endocervix, *N. gonorrhoeae* is rarely isolated from the cul-de-sac. In a very real sense, the way one recovers from gonococcal infection, in the absence of antibiotic therapy, is by bacterial interference engendered by the anaerobic progression. However, the price of bacterial interference is structural damage.

The presence of a foreign body within the endometrial cavity may or may not exert an influence on the sequence of events. The alterations due to mechanical factors (i.e. the induction of predecidual changes, microerosions of the mucosa, and the presence of a chronic inflammatory cell infiltrate), if not associated with concomitant chronic anaerobic bacterial infection, may accelerate the anaerobic progression in patients with gonococcal salpingitis. If there is an antedating anaerobic bacterial infection associated with the presence of an intrauterine device (IUD), fallopian tube involvement is more likely to be due to Class II anaerobes, and in particular to members of the *Bacteroidaceae,* rather than to *N. gonorrhoeae*.

The anatomic lesions of the fallopian tube are intraluminal as well as interstitial (Figure 75.1a and b). Because of the volumetric expansion of the interstitium, owing to edema fluid, hyperemia, and the presence of an inflammatory infiltrate, the finger-like mucosal intraluminal projections are brought into proximity (Figure 75.1c and d). While an intense inflammatory exudate is present within the intraluminal space, it is thought that the interstitial microabscesses immediately beneath the mucosal basement membrane

are a critical factor in determining whether or not residual damage will ensue (Figure 75.1e). These microabscesses are probably not due to *N. gonorrhoeae* but rather to superinfecting anaerobic bacteria from the vaginal flora. As long as the basement membrane is intact, mucosal regeneration is possible. Once the basement membrane is destroyed, the inevitable consequence is healing by fibrosis. The destruction of the basement membrane of two opposed mucosal surfaces leads to the establishment of inflammatory bridges. The ultimate consequence of basement membrane destruction is a permanent structural alteration of the fallopian tube architecture.

Clinically, patients will have a significant endocervical or vaginal discharge owing to the presence of the intense inflammatory response elicited by *N. gonorrhoeae*. With progressive fallopian tube involvement, the patient experiences initially intermittent crampy lower abdominal pain. Secondarily, there is heightened autonomic peristaltic activity of the muscularis in response to a relatively non-flexible submucosal inflammatory edema. The clinical perception of pain may be heightened by the focal inflammatory neuritis. While there may be a significant extension of the inflammatory process into the muscularis, peritonitis, when it ensues, in most instances is the consequence of purulent material issuing from the fallopian tube. Depending upon the quantity of material reaching the peritoneal surface, the patient may perceive a change in the character of the pain, which is now sharper, more constant, and likely to be exacerbated by positional changes.

In the majority of instances the inflammatory exudate which reaches the peritoneal cavity sequesters within the cul-de-sac. In isolated instances significant amounts of pus reach the right posterior gutter and ultimately the perihepatic region. The clinical manifestations which ensue depend upon whether the suprahepatic or infrahepatic portion of Glisson’s capsule is involved. If infracapsular infection involves the serosal surface of the gallbladder, right upper quadrant pain may ensue,

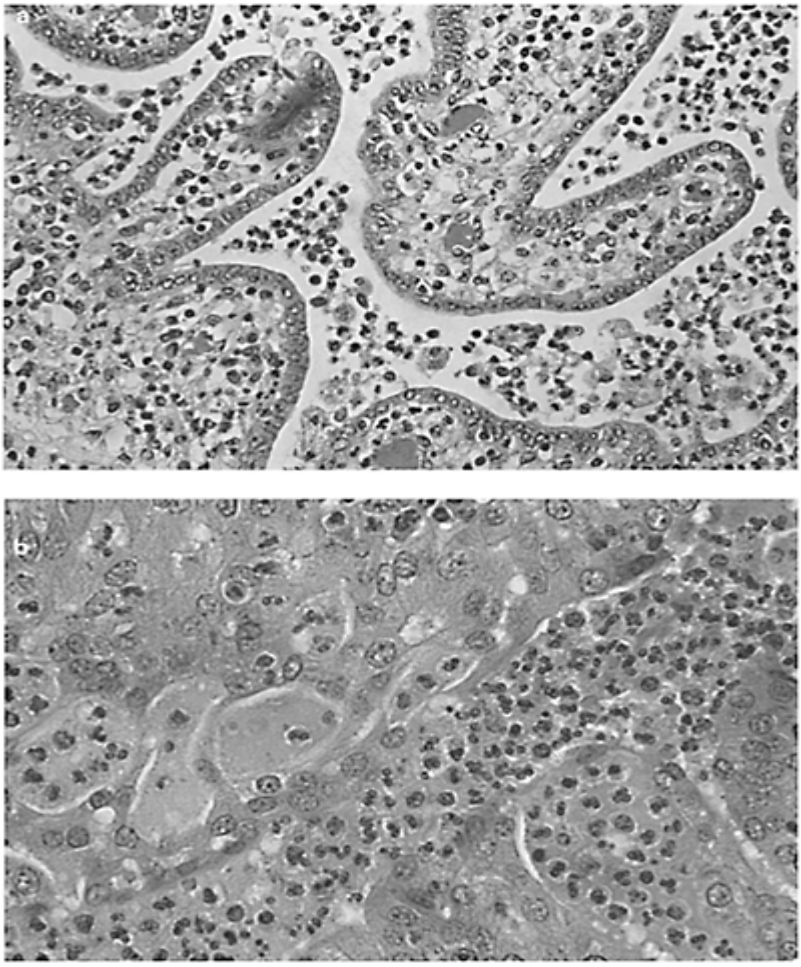

Figure 75.1 Bacterial replication and the resultant inflammatory response within the fallopian tubes in salpingitis. (a) Lesions involve both intraluminal and interstitial sites (H&E, ×175). (b) With intensification of the inflammatory process, microabscesses (presumably due to superinfecting anaerobic bacteria) develop at the interstitial site, ultimately resulting in basement membrane destruction (H&E, ×234).

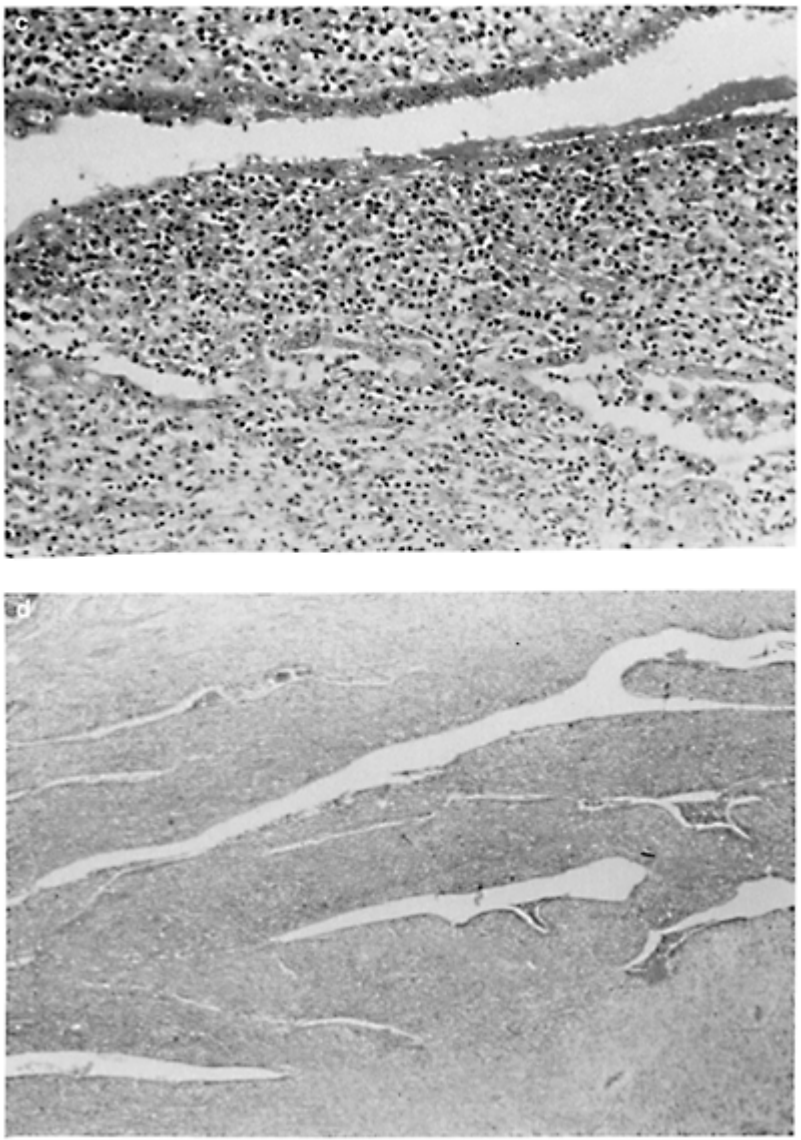

Figure 75.1 (c, d) With basement membrane destruction (particularly when two such areas are opposed), the potential for the creation of an inflammatory bridge has been achieved (H&E, ×240 and ×110).

Figure 75.1 (e) With repeated episodes the fallopian tube undergoes structural alterations which may significantly alter its functions of transport and nutrition of the fertilized ovum (H&E, ×105)

with a pattern of radiation which mimics that observed in cases of acute cholecystitis. Suprahepatic involvement may produce supraclavicular pain.

CHLAMYDIAL SALPINGITIS

Chlamydial salpingitis has always been part of the sexually transmitted disease (STD) spectrum. In 1732, John Astruc (Figure 75.2) wrote, based upon observations of Parisian prostitutes, of a chronic form of salpingitis which

> *'occurs in women whose uterus is thrown into contractions by lascivious ticklings and by excess of prostitution. Many have no pain, but the infection in time injures the internal surface of the uterus and its tube.'*

In contrast to gonococcal salpingitis, chlamydial tubal infection can produce a true chronic subclinical infection. Intracellular chlamydial organisms may persist in the genital tissues for extremely long periods of time and continue to produce silent progressive tubal damage. When infertile patients with chlamydial antibodies are

evaluated with laparoscopy, frequently no history of an illness or procedure can be elicited which could explain the presence of post-inflammatory tubal damage.

Cultural and serologic data have built an extensive case for *C. trachomatis* as both an etiologic agent and a potential co-pathogen in acute salpingitis. Chlamydial cervicitis is present in 20–40% of patients with acute gonococcal salpingitis.

In contrast to 'classical PID' due to *N. gonorrhoeae,* chlamydial disease tends to be more occult (Table 75.2). Sometimes only vague peritoneal pain precipitated by jarring movements is the prime factor motivating the patient to seek medical attention. Characteristically, the temperature is less than 38ºC. The principal findings on pelvic examination are cervical motion tenderness and varying degrees of cervicitis.

The role of chlamydia in acute salpingitis is not clearly understood. *C. trachomatis* appears to be able to both initiate infection and pave the way for bacterial superinfection and function as a monoetiological pathogen. Both mechanisms will produce involuntary infertility.

Figure 75.2 John Astruc, MD
(Courtesy of National Medical Library, Bethesda, Maryland)

While the degree of overlap in the clinical presentation in chlamydial and gonococcal-related salpingitis is extensive, some unique demographic characteristics do exist. Unless pre-existing infection with *Trichomonas vaginalis* is present, disease due to *N. gonorrhoeae* characteristically occurs in close proximity to the menstrual period. The occurrence of chlamydial salpingitis is more scattered with its mean peak incidence delayed about four to seven days, compared to patients with gonococcal salpingitis. Patients with chlamydial disease tend to appear less toxic. The fever elevation and white blood cell count (WBC) characteristically are lower. Patients with stage I or stage II salpingitis will have an erythrocyte sedimentation rate which is below that anticipated for patients with a comparable stage of gonococcal disease.

There is a significantly higher incidence of chlamydial disease among users of oral contraceptives. These patients often have a prior history of Krettek's syndrome ('breakthrough' intramenstrual bleeding which responds to doxycycline therapy).

PROXIMAL STUMP SALPINGITIS

Despite anatomical interruption of the fallopian tubes, the proximal remnants of the fallopian tubes are vulnerable to ascending infection. Proximal stump salpingitis does not present with classical signs and symptoms. Fletcher reported five cases of disease arising in the proximal remnants of the fallopian tubes. The majority of these patients presented with unilateral pain. Physical examination demonstrated exquisite adnexal tenderness. Of note were the relatively normal WBC encountered.

OTHER MONOMICROBIAL ETIOLOGIES

There are at least two organisms capable of producing acute salpingitis in addition to *N. gonorrhoeae*. These are the group A beta-hemolytic streptococci and *Neisseria meningitidis*.

Group A beta-hemolytic streptococci

Monif *et al*. have demonstrated that, in isolated instances, *Streptococcus pyogenes* can be a monoetiologic cause of acute salpingitis. The recovery of the organism and the ability to exclude the concomitant presence of Class III anaerobes has focused on the probability that the group A streptococci, under selective conditions, can be a rare cause of acute salpingitis in the non-pregnant woman. Although they are bacteria of unique virulence, the group A streptococci require a specific event such as a mechanical disruption of the cutaneous and mucosal barrier to initiate overt infection. The onset of menstruation appears to be an effective initiating event, and consequently the disease is proximate to the onset of the menses in a manner which is not dissimilar to that characteristic of *N. gonorrhoeae*. The clinical manifestations are indistinguishable from those associated with *N. gonorrhoeae*.

Table 75.2 Comparison of gonococcal and chlamydial salpingitis

Parameter	*Gonococcal salpingitis*	*Chlamydial salpingitis*
Mode of contraception	More likely to be IUD or none	More likely to be oral contraceptive
Prior history of mid-cycle 'break-through bleeding'	Unlikely, unless IUD in place	Occurs in a significant number of cases
Presentation	Acute	Subacute to semi-acute
Relationship to menses	Closely associated; if *T. vaginalis* is present, disease may occur later in the menstrual cycle	May occur at any time in the cycle
WBC in Stages I and II	Tends to be more elevated	
ESR in Stages I and II	Somewhat elevated	Tends to be normal

ESR, erythrocyte sedimentation rate; WBC, white blood cell count; IUD, intrauterine device

The incidence of acute salpingitis due to the group A streptococcus is low. Monif *et al.* identified a single case in a study of 92 patients with acute salpingitis. Eschenbach *et al.*, in their study of 241 cases of acute PID, recovered *S. pyogenes* from the cul-de-sac in a single instance. In their case, as in that reported by Monif *et al.*, a pure culture of group A beta-hemolytic streptococci was recovered from the cul-de-sac.

Neisseria meningitidis

On rare occasions, *N. meningitidis* can be recovered from the endocervix. Epidemiologic delineation of its possible role as a pathogen for the female genital tract has been basically negated. Unlike the case in oropharyngeal infection, carbohydrate fermentation or immunofluorescence is not required for genital tract isolates to establish the diagnosis of *N. gonorrhoeae* infection. The Centers for Disease Control accepts the presumptive criteria for the identification of *N. gonorrhoeae* as being diagnostic in a definitive sense for such isolates. In the course of their studies of the bacteriology of the cul-de-sac isolates in acute salpingitis, Monif *et al.* have recovered *N. meningitidis* from the cul-de-sac of a patient with presumably gonococcal endocervicitis and polymicrobial peritonitis.

In both group A streptococcal and *N. meningitidis* acute salpingitis, the diagnosis is readily established by cultures of the endometrium and a culdocentesis specimen. Neither the group A streptococci nor *N. meningitidis* present therapeutic problems. Both organisms respond readily to penicillin and its semisynthetic analogs. If the new-generation tetracyclines are used, a given isolate of group A streptococci may not respond.

Streptococcus pneumoniae

Streptococcus pneumoniae is not a normal constituent of vaginal bacterial flora; however, given the opportunity, *S. pneumoniae* can be a significant pathogen for the female genital tract.

Involvement of the female genital tract as a metastatic process secondary to maternal septicemia due to *S. pneumoniae* is a relatively well-documented phenomenon in the preantibiotic era. The occurrence of cases of chorioamnionitis and/or perinatal septicemia in the absence of pulmonary involvement indicated the possibility of contiguous spread from the vaginal/cervical reservoir and subsequent involvement of the female upper genital tract.

Genital tract disease due to *S. pneumoniae* has been reported in non-pregnant females. Isolated cases of spontaneous pneumococcal peritonitis have been described. Hadfield *et al.* reported a case of a 46-year-old woman with bilateral tubo-ovarian masses. Biopsy specimens from both tubes and from the wall of the abscesses demonstrated Gram-positive, lance-shaped diplococci which were documented to be *S. pneumoniae* by immunoperoxidase staining. Rahav *et al.* reported a case of postmenopausal pneumococcal tubo-ovarian abscess from which *S. pneumoniae* was recovered. The fallopian tubes in these two cases of spontaneous peritonitis due to *S. pneumoniae* were described as being swollen and hyperemic with pus emanating from the ends. What was described is not a specific disease entity (spontaneous peritonitis) but more probably a progressive consequence of salpingitis. Patterson *et al.* have subsequently reported a case of pneumococcal salpingitis documented by laparscopy.

Incrimination of *S. pneumoniae* as an etiological agent in cases of acute salpingitis is probably an under-reported phenomenon. While *S. pneumoniae* will grow on 5–7% sheep blood agar culture when incubated in a CO_2 environment, the recovery of alpha-hemolytic streptococci is usually not worked up any further and is often reported as ‘mixed vaginal flora’. Recovery of alphahemolytic streptococci from patients with acute salpingitis needs to be microbiologically evaluated to exclude the possibility that these isolates are *S. pneumoniae*.

Haemophilius influenzae

In rare cases, *H. influenzae* appears to be the causative agent for tubo-ovarian abscess or salpingitis. Most cases of serious gynecologic infections caused by *H. influenzae* reported previously have occurred in association with an IUD. Recently Carmeci and Gregg reported a case of acute salpingitis which was not associated with an IUD or any other predisposing conditions like *S. pneumoniae*. When *H. influenzae* is a cause of salpingitis, septicemia commonly occurs.

BACTERIOLOGY OF GONOCOCCAL AND NON-GONOCOCCAL ACUTE SALPINGITIS

The bacteriologic isolates derived from the cul-de-sacs of 92 patients studied at the University of Florida College of Medicine are listed in Table 75.3. When the 269 bacterial isolates were grouped in accordance with the Gainesville Classification, 215 aggregated in Category I (Gram-positive aerobes and those bacteria with demonstrable susceptibility to penicillin). Since the majority of the group D streptococci (enterococci) are susceptible to penicillin, one can readily appreciate why the majority of patients did well on single-drug penicillin therapy, particularly when the penicillin was given in doses of 10 to 20 million units/day. Bacteriological data derived from the cul-de-sacs of women with acute salpingitis has well substantiated the distribution of bacterial isolates.

One of the major reservations which must be retained in interpreting the significance of a given bacterial isolate from the cul-de-sac is that the data reported are neither qualitative nor quantitative. The critical factor which determines whether or not a bacterial isolate may have potential significance appears to be the oxidation-reduction potential. At any given moment, one organism may be more significant than another in the presumed bacterial synergism which is postulated in the anaerobic progression. Unless the anaerobic microbiologic environment of the cul-de-sac is in a critical zone, the more aerobic portion of the anaerobic progression is the focus of therapy. If no further alteration is required to achieve the required redox potential, eradication of the total cul-de-sac flora is required in order to achieve the anticipated therapeutic response.

DIAGNOSIS

Traditionally, there are certain physical findings which are typical in acute salpingitis. While the abdominal symptoms are common to a number of disease processes, pelvic examination is often characteristic. The presence of exudate issuing from the endocervix, marked uterine tenderness, and exquisite cervical tenderness to motion are all physical findings characteristic of patients with acute salpingitis. One often neglected differential point in acute salpingitis is the obtaining of serial temperatures. If a temperature is obtained within 20 minutes before doing a bimanual pelvic examination and then retaken every 15 minutes for the next 45–60 minutes, a significant number of patients with acute salpingitis are found to exhibit a precipitous elevation in temperature. In these instances, the pelvic examination is a challenge test.

Unfortunately, one has been traditionally geared to the stereotypic picture of acute salpingitis. Our perception of a chronic variant which is perhaps of greater importance in terms of structural damage periodically lapses from recognition.

While the diagnosis of acute salpingitis can be made with a high probability of accuracy, the same cannot be said for those patients with a subacute or *forme fruste* variant. Making the diagnosis of such upper genital tract

Table 75.3 Bacteriologic spectrum of isolates from the cul-de-sacs of 64 patients with endometritis-salpingitis-peritonitis*

Organism	*No. of isolates*	*Organism*	*No. of isolates*
GROUP I A. Aerobes and facultative bacteria Streptococci, not group D		Gram-positive non-sporulating (GPNS) rods	
alpha-hemolytic streptococci	16	*Eubacterium* spp.	2
non-hemolytic streptococci	12	*Eubacterium lentum*	2
beta-hemolytic streptococci, Group B	4	*Eubacterium tenue*	1
Lactobacilli	2	*Eubacterium aerofaciens*	1
Microaerophilic streptococci	8	*Eubacterium contortum*	1
Corynebacteria	12	*Propionibacterium acnes*	1
Staphylococci		*Propionibacterium avidum*	1
coagulase-negative	8	*Lactobacillus* spp.	1
coagulase-positive	3	*Lactobacillus salivarius*	1
Micrococci	1	*Lactobacillus acidophilus*	1
Eikenella corrodens	1	*Lactobacillus minutus*	1
Neisseria gonorrhoea	17	*Lactobacillus fermentum*	1
Total aerobes	84	*Bifidobacterium* spp.	1
		Bifidobacterium infantis	3
B.Anaerobes		*Bifidobacterium longum*	1
Peptococci		*Bifidobacterium adolescentis*	1
Peptococcus spp.	17	Unidentified GPNS rods	12
Peptococcus morbillorum	2	Total GPNS	32
Peptococcus prevotii	11		
Peptococcus asaccharolyticus	4	Total anaerobes	123
Peptococcus variabilis	1		
Total peptococci	35	Total group 1	207 (76.9%)
Peptostreptococci		GROUP II *Bacteroides fragilis*	
Peptostreptococcus spp.	17	ss. *fragilis*	5
Peptostreptococcus anaerobius	9	ss. *ovotus*	1

Peptostreptococcus productus	1	ss. *thetaiotaomicron*	2
Peptostreptococcus micros	2	ss. *distasonis*	2
Total peptostreptococci	29	ss. *vulgatus*	1
		ss. unknown (‘no good fit’)	12
Veillonella	6	ss. not determined	2
Unidentified Gram-negative cocci	2	Total Group II	24 (8.9%)
Bacteroides species other than *fragilis*			
Bacteroides spp.		GROUP III Group D streptococci (enterococci)	12 (4.5%)
Bacteroides corodens	1		
Bacteroides pneumosintes	3		
Bacteroides nodosus	1	GROUP IV *Enterobacteriaceae*	
Bacteroides melaninogenicus ss. intermedius	2	A.Escherichia *coli*	8
		Serratia marcescens	2
Bacteroides cappillosus	4	*Proteus mirabilis*	1
Bacteroides oralis		*Enterobacter cloacae*	1
Total bacteroides	23	*Klebsiella pneumoniae*	3
		Citrobacter diversus	1
Fusobacterium spp.		Total *Enterobacteriaceae*	16
Unidentified Gram-negative rods	3		
Clostridia		B. Others	
Clostridium spp.	2	*Gardnerella vaginalis*	9
Clostridium malenominatum	1	*Gardnerella influenzae*	1
Clostridium haemolyticum	1	Total other	10
Total clostridia	4	Total Group IV	26 (9.7%)
		Total isolates in all 4 therapy groups	269

*Bacterial isolates are grouped by the Gainesville Classification (Monif GRG, *et al. Excerpta Medica* 1977; 3:26)

Table 75.4 CDC pelvic inflammatory disease (PID) clinical case definition

A clinical syndrome resulting from the ascending spread of microorganisms from the vagina and endocervix to the endometrium, fallopian tubes, and/or contiguous structures. **All of the following clinical criteria must be present:**

- Abdominal direct tenderness
- Tenderness with motion of the cervix
- Adnexal tenderness

In addition to all of the above criteria, **at least one of the following findings must also be present:**

- Oral temperature>38° Celsius
- Abnormal cervical or vaginal discharge
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*
- Histopathologic evidence of endometritis on endometrial biopsy
- Radiologic abnormalities (thickened fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex) on transvaginal sonography or other radiologic tests
- Laparoscopic abnormalities consistent with PID
- **Leukocytosis>10000 WBC/mm^3**
- Purulent material in the peritoneal cavity obtained by culdocentesis or laparoscopy
- Pelvic abscess or inflammatory complex on bimanual examination or by sonography

infections without resorting to invasive procedures such as an endometrial biopsy or laparoscopy is difficult.

In patients with subacute salpingitis, the onset of symptoms is independent of the menstrual cycle. If febrile temperatures occur, rarely do they exceed 38ºC. Not infrequently there is a history of antibiotic therapy in the past, particularly for urinary tract infection. The patients tend to be more chronically than acutely ill. What is characteristic is that they have had a recent history of lower quadrant pain which is usually the reason they seek medical consultation. Physical examination often demonstrates little save for cervical tenderness which may or may not be associated with a discharge. If one does a jar test (which is performed by asking the patient to stand on her tiptoes and then suddenly drop to her heels) and peritoneal pain is apparent, culdocentesis not infrequently will demonstrate the presence of purulent material from which a polymicrobial flora can be isolated.

Up to one-third of patients with laparoscopically confirmed salpingitis neither had an elevation of temperature above 38ºC nor had evidence of a leukocytosis. The erythrocyte sedimentation rate (ESR) is of value only if significantly elevated. A markedly elevated

ESR should suggest the possibility of tubal occlusion or tubo-ovarian complex. A normal ESR with a tubo-ovarian complex should suggest a chlamydial etiology.

The Centers for Disease Control (CDC) has developed a clinical case definition which encompasses the majority of these points (Table 75.4). The major adjunctive diagnostic procedures which are done in cases of acute salpingitis are:

(1) staging of the disease, and, if signs of peritoneal irritation are present; and
(2) obtaining Gram stains and cultures of the endocervix and the endometrium for *N. gonorrhoeae* and *C. trachomatis*.

No one laboratory test (serum WBC, vaginal leucocytosis, C-reactive protein (CRP) or ESR) has validity in terms of sensitivity or negative predictive value. Part of the problem is the failure to analyze patients with overt acute salpingitis separately from those individuals with the subacute or chronic variants. Peipert *et al.* analyzed 120 women who either met the Centers for Disease Control and Prevention's minimal criteria for acute PID or who had other signs of upper genital tract infection (i.e. atypical pelvic pain, abnormal uterine bleeding, or cervicitis). Sensitivities for elevated WBC, ESR, CRP, and increased vaginal white blood cells are 57, 70, 71 and 78% respectively. If any one test is abnormal, the sensitivity is 100% and specificity is 18%. If all four tests are abnormal, sensitivity is 29% and specificity is 95%. When all laboratory tests were normal, objective evidence of upper genital tract infection was not found.

Testing for increased vaginal white blood cells was found to be the most sensitive laboratory indicator for upper genital tract infection, whereas serum WBC was the most specific. No one diagnostic laboratory test is pathognomonic for upper genital tract infection. Combinations of positive tests can improve diagnostic specificity and positive predictive value, but with a diminution of sensitivity and negative predictive value.

In a meta-analysis of 12 studies assessing laboratory criteria for the diagnosis of PID, Kahn *et al.* found that CRP was significantly predictive in the four studies in which it was part of the data collected. The test displayed good sensitivity (74–93%) with a range of specificity (50–90%). ESR was found to be a significant indicator of upper genital tract infection. When the ESR was greater than 25 mm/hour, its sensitivity was 55% and specificity 84%.

Miettinen *et al.* evaluated the ESR and CRP in assessing the severity of acute salpingitis. Separately, they were unacceptable in terms of sensitivity and negative predictive value. When used together (i.e. either test abnormal), both sensitivity and negative predictive value improved to 96 and 97% respectively, with a decrease in specificity to 61% and maintenance of positive predictive value at 70%. The cutoff levels Miettinen *et al.* used were high: ESR greater than 40 mm/hour and CRP greater than 60 mg/dl.

In general, CRP determinations are of little diagnostic use; however, when elevated, they are of value in determination of the duration of short-term parenteral antibiotic therapy. In Stage II salpingitis, the mean CRP should be decreased by the third day of treatment. CRP level becomes normal much sooner than does the ESR and consequently becomes useful predictor of the short-term response to antimicrobial therapy.

The ESR can be normal despite a tubo-ovarian complex when the etiological agent is *C. trachomatis*.

An ESR of greater than 50 mm/h should alert the clinician to the probable presence of significant tubal occlusion or a definite tubo-ovarian complex.

While the presence of vaginal white blood cells on wet mount analysis increases the probability of genital tract infection, the use of a Q-tip swab sampling of the endometrial cavity is advocated. The sample is a smear on a glass slide and stained. The presence of a significant inflammatory component correlates better with the presence of endometritis and with corroborating physical findings of endometritis/salpingitis.

Laparoscopic confirmation is the gold standard for diagnosing salpingitis. The use of laparoscopy to attain visual evidence of salpingitis is both expensive and not without risk to the patient. Laporoscopy is best reserved for PID (Physical-In-Doubt or Pretty Inadequate Diagnosis).

Unless a tubo-ovarian complex has ruptured, blood cultures are rarely positive. The use of culdocentesis is largely restricted to situations where clinical ambiguity exists or to obtain cul-de-sac specimens for research studies.

THERAPY

Acute salpingitis

Beyond the eradication of disease and infection, therapeutic success for the female must involve preserving fallopian tube structure and function.

In 1917, William Osler was quoted as saying that *'the gonococcus is not a great destroyer of life, but as a misery producer Neisser's coccus is king among germs.'* For Osler, the morbidity of disease was to be found in the *'chronic pelvic mischief and unhappiness in sterile marriages.'* The intervening seven decades have done little to alter the validity of his observation. Therapy in the 1990s must encompass preservation of fallopian tube structure and function or, in the cases of advanced disease, preservation of ovarian function by precluding the need for surgical intervention.

In the early 1970s, Westrom demonstrated by laparoscopic evaluation a 12.8% incidence of tubal occlusion following a single episode of acute salpingitis. Following two episodes, the figure increased to 35.5% and

Table 75.5 Incidence of tubal occlusion documented by laparoscopy following one, two or three episodes of acute salpingitis

Number of episodes of acute salpingitis	*Am] Obstet Gynecol 1975; 121:707*	*Am J Obstet Gynecol 1980; 131:880*
One	12.8%	11.4%
Two	35.5%	23.1%
Three	75%	54.3%

following three episodes to 75%. When the same investigator re-evaluated the impact of an expanded therapeutic armamentarium on fallopian tube morbidity, the observed

incidence of tubal occlusion following one, two and three episodes of acute salpingitis were 11.4%, 23.1% and 54.3%, respectively (Table 75.5).

The probability of secondary infertility is statistically linked to age, number of antecedent episodes of acute salpingitis, and severity of disease at the time of institution of appropriate antibiotic therapy. The incidence of infertility was reduced irrespective of the number of prior episodes of acute salpingitis in 15 to 24-year-old women as opposed to 25 to 34-year-old women. In women less than 25 years of age, those who had had gonococcal-associated salpingitis had a significantly better fertility prognosis than those who had had non-gonococcal salpingitis.

When the degree of the inflammatory reaction documented by laparoscopy is correlated with subsequent reproductive outcomes, a positive increase in correlation can be demonstrated. Viberg has demonstrated that early effective antibiotic therapy gives the shortest value of ESR half-time. No involuntary infertility occurred in patients who received early antibiotic therapy and demonstrated a good therapeutic response.

In treatment of STD, we should be looking for an antimicrobial regimen which provides a cure at least 95% of the time while preserving anatomic structure and function.

The CDC guidelines identify a number of therapies which in clinical trials have been shown to be efficacious. What is wrong in the therapeutic studies in the literature is the aggregation of all stages of acute salpingitis by virtue of nomenclature, but numerical dominance of patients with Stages I and early II in the treatment groups. By the overload of patients who will respond to any regimen effective against all isolates of *N. gonorrhoeae* and *C. trachomatis* (e.g. selected fluoroquinolones), FDA approval is achieved for drug regimens which inadequately deal with anaerobic superinfection.

Tubo-ovarian complex/abscess

The diagnosis of a tubo-ovarian complex (TOC) may be inferred by a physical examination but ultimately is contingent on the use of ultrasonography laparoscopy or computerized tomography. More recently magnetic resonance imaging has been successfully used to demonstrate the extent of the disease, characterize the lesion and demonstrate involvement of adjacent pelvic organs. this technology has some applicability when attempting to differentiate Stage III (TOC) from Stage IV (rupture TOC) salpingitis. When attempting to distinguish pelvic masses, transvaginal color Doppler sonography may help diagnostically and prognostically, Fleischer *et al.* demonstrated that 72% of masses with high impedance underwent regression, whereas only 21% of lesions with low impedance did. Only 20% of masses demonstrating low impedance or morphologically complex structure regressed. Sixty-five percent of lesions that regressed had a significant drop in pulsatility index. Probability of regression was the greatest in young women (less than 40 years of age) and in masses <5 cm.

Therapy of women with TOCs or tubo-ovarian abscesses (TOAs) involves antibiotic therapy which encompasses the STD spectrum of pathogens as well as the bacteria within the anaerobic progression. Large complexes and complexes whose tenderness persists despite 48 hours of appropriate antibiotic therapy should be considered as possible candidates for lesion aspiration under sonographic guidance. Women with ovarian involvement or persisting signs of peritoneal irritation or positive blood cultures for enteric Gram-negative rods usually require prompt surgical intervention.

When a TOC has been documented by ultrasonography, the mass remains significantly tender despite appropriate antibiotic therapy at the end of 48–72 hours, and no evidence of peritoneal irritation is demonstrable, serious consideration should be given to ultrasound-guided transvaginal drainage of the TOC. Perez-Medina *et al.* prospectively compared the outcome after TOC with intensive antibiotic therapy. Patients were assigned to two groups, distributed on a random basis, with a clinical and ultrasound diagnosis of TOA of less than 10 cm maximal diameter. Both groups received an antimicrobial combination of clindamycin and gentamicin. In the study group, they performed early transvaginal drainage of the abscesses. Both short-term (48–72 h) and medium-term (4 weeks) responses to the treatment were evaluated. In the study group a favorable short-term response was observed in 90% of the cases, whereas this was 65% in the control group. Caspi *et al.* used single-step ultrasound-guided aspirations in conjunction with intracavity antibiotic instillation for the treatment of 10 women with TOA who failed to respond to systemic antibiotic therapy. All ten women improved clinically and none required surgery. The mean time from aspiration to hospital discharge was 3.1 days with mean duration of hospitalization 7.8 days. No major complications were observed. The average time interval between aspiration of the lesion and resolution on sonographic follow-up was 9.5 weeks. In three cases, PID recurred, but none needed surgical intervention.

HIV infection and salpingitis

Barbosa *et al.* studied cross-sectionally 349 women hospitalized with salpingitis at an urban hospital serving a population at high-risk for HIV. Among the 349 women with PID, 27 were HIV-positive. These HIV-positive women had lower mean WBC at admission (7411 versus 11266, $p<0.01$), lower mean lymphocyte counts (1411 versus 1928, $p<0.01$), greater febrile morbidity (54 versus 28.3%, $p<0.01$), and longer hospital stays (10.5 versus 6.4 days, $p<0.01$) than HIV-negative women. Women who were HIV-positive required more time for defervescence and needed to change their antibiotic regimen more frequently (41 versus 12.7%, $p<0.01$).

THERAPEUTIC REQUISITES FOR ANTIBIOTIC SELECTION IN ACUTE SALPINGITIS

For more than three decades, the therapy of acute salpingitis was influenced by monomicrobial genesis of its counterpart in males and its implied corollary, antimicrobial selection predicated on drug of choice concept. The mandate for change came from two independent sources which ultimately converged to formulate the current basis for therapeutic recommendations:

(1) recognition of polymicrobial super-infection; and
(2) recognition of polymicrobial etiology.

Polymicrobial superinfection

The utilization of culdocentesis coupled with the application of sophisticated anaerobiology gave investigators the opportunity to look at what could be construed as both the front and the back of the conduit and make a sophisticated guess as to what was happening in the middle. A significant number of women with gonococcal endocervicitis have been shown to have a polymicrobial peritonitis at the other end of the conduit (cul-de-sac).

From bacteriological observations, the concept of polymicrobial superinfection of initial gonococcal salpingitis was developed. *N. gonorrhoeae,* by virtue of its replication, sufficiently lowers the oxidation-reduction potential of the local microbiological environment so as to initiate the anaerobic progression. This process is the mechanism by which a monomicrobial process becomes polymicrobial disease.

As the progressive changes in the microbiological environment select for the more microaerophilic organisms (Class II anaerobes), *N. gonorrhoeae* undergoes auto-elimination. This process of auto-elimination which occurs in the cul-de-sac also occurs in the fallopian tubes, endometrium, and endocervix. Ultimately, a situation arises where the gonococcus cannot be recovered from either end of the conduit. When nonrecovery of *N. gonorrhoeae* can be excluded because of technical problems (delayed plating, use of cold modified Thayer-Martin plates, the absence of initial ambient carbon dioxide, etc), the absence of the gonococcus has come to imply either infection caused by *C. trachomatis* or advanced disease as a result of anaerobic superinfection of initial gonococcal salpingitis. The ability to achieve the anticipated therapeutic response is significantly altered in patients with advanced polymicrobial superinfection.

Ideally, antimicrobial therapy of any infection should be based on the identification of the causative organism in specimens taken from the infected site and the sensitivity of these isolates to the antimicrobial agent. The inability to culture the critical site of organism replication, the fallopian tubes, predicates that the treatment regimens instituted must cover the broad range of the pathogenic spectrum which participates in the anaerobic progression as well as the primary STD spectrum.

Chlamydia trachomatis

The selection of antibiotic therapy for acute salpingitis is complicated by the potential etiologic diversity. *C. trachomatis* is the most common cause of STD in many countries. The frequency of isolation from the cervix of women with acute salpingitis is between 5 and 40%. In a limited series, the organism has been recovered from the fallopian tubes or peritoneal exudate in up to 30% of cases of acute salpingitis. A significant change in antichlamydial antibody titer can be documented in 18–40% of women with acute salpingitis. *C. trachomatis* can be concomitantly isolated with *N. gonorrhoeae* in 20–40% of patients with gonococcal infection. Any antimicrobial regimen used to treat women with gonococcal infection should be effective against *C. trachomatis*. While latency can be induced by penicillin and its semisynthetic analogues, the organism is usually not eradicated by beta-lactam antibiotics. The drug of choice is a tetracycline antibiotic. *C. trachomatis* is an important etiologic agent in acute salpingitis. Irrespective of the agent

isolated from the cervix, antichlamydial activity should be an integral part of any therapeutic regimen used.

Polymicrobial etiology

When polymicrobial infection evolves, if structural damage to the fallopian tubes is to be minimized, it may be imperative to eradicate all bacterial constituents. While it has been shown that, early in the course of the anaerobic progression, partial interruption of the synergism is often effective in aborting the ensuing evolution of strict anaerobic infection, once the polymicrobial infection is established, it may be possible for more than one organism to capitalize on the alteration which has been induced.

Penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG)

A third factor that has entered into the therapeutic equation is the increasing prevalence of the penicillinase-producing strains of *N. gonorrhoeae* (PPNG). Chromo-somal mutation has accounted for the stepwise increase in the resistance of *N. gonorrhoeae* to penicillin observed since 1943. Plasmid-mediated resistance is directly related to the production of beta-lactamase, which is coded for by either a 3.3 megadalton plasmid (West African origin) or a 4.4 megadalton plasmid (Southeast Asian origin). The spread of the PPNG strains has forced a major reformulation of our current therapeutic recommendations.

The critical issue in the therapy of acute salpingitis goes beyond the treatment of the complexity of monomicrobial disease or infection; it involves the prevention or eradication of bacterial superinfection. A growing body of data indicates that the secondary anaerobic invaders and not *N. gonorrhoeae* are the principal agents responsible for basement membrane destruction and resultant healing by fibrosis.

Antibiotic selection is governed by the need to accommodate polymicrobial etiology, polymicrobial superinfection, and PPNG, when possible, into a single therapeutic regimen. Since the ultimate goal of the therapy of acute salpingitis is preservation of fallopian tube structure and function, a regimen cannot be instituted and subsequently corrected if the anticipated therapeutic response does not materialize in a specific time. It is quite probable that appropriate antibiotic

Table 75.6 Gainesville staging of acute salpingitis

Stage	***Therapeutic goal***
I—Acute salpingitis without peritonitis (ES)	Eradication of symptomatology and ineffectivity
II—Acute salpingitis with peritonitis (ESP)	Preservation of fallopian tube structure and function
III—Acute salpingitis with evidence of tubal occlusion or tubo-ovarian complex	*Primary therapeutic goal:* Preservation of ovarian function
IV—Ruptured tubo-ovarian complex	*Primary therapeutic goal:* Preservation of life

therapy in the first 24 hours is the critical determinant in preserving fallopian tube structure and function.

THERAPEUTIC STAGING OF ACUTE SALPINGITIS

The intent of nomenclature or classification is to render meaning or clarity to a given set of facts or concepts. Without individualization of treatment and delineation of appropriate stages of disease, the consequences for women have been unwanted secondary infertility, ectopic pregnancies, increased occurrence of TOCs, and possible surgical removal of the genital organs. Each state of disease can be differentiated by virtue of its major therapeutic goal and the means by which this goal can be achieved (Table 75.6). Although an inverse therapeutic correlation is documentable between achieving the anticipated therapeutic response with single-drug therapy effective against both *N. gonorrhoeae* and *C. trachomatis* and increased stage of disease, the ability to achieve the anticipated therapeutic response with recommended therapy of the Gainesville staging has been demonstrated for Stages I and II.

Papavarnavas *et al.* compared the accuracy of the Gainesville staging with laparoscopic findings. The clinical staging of acute salpingitis correlated with laparoscopic findings in 82.6% of cases, and when the diagnosis was correct the severity of the clinical staging correlated with that of laparoscopic staging as the probability increased of polymicrobial superinfection. Staging is a guideline for the initiation of therapy and setting of priorities. Failure to achieve the anticipated therapeutic response requires aggressive reassessment of clinical management.

Stage I—acute salpingitis without peritonitis

In Stage I disease, barring the presence of PPNG, patients without peritonitis or an IUD who have no underlying structural damage to the fallopian tubes show excellent response to the penicillins or the tetracyclines. When patient compliance can be assured, these patients can be treated on an outpatient basis; however, we prefer to hospitalize all patients for whom future fertility is an important issue. The presence of an IUD in a patient with Stage I disease warrants hospitalization.

Stage II—acute salpingitis with peritonitis

A patient with Stage II disease is clinically similar to a woman with Stage I disease, except that bilateral lower quadrant rebound tenderness is demonstrable. The therapeutic goal for Stage II disease is the preservation of fallopian tube structure and function. Stage II is documented by the demonstration of peritonitis by physical examination in patients with Stage II disease; if the gonococcus is a constituent of the polymicrobial bacterial flora, the probability of achieving the anticipated therapeutic response is approximately 60%. If the gonococcus is not present, the probability drops to 30%. In Stage II disease, the gonococcus, although important in the induction of the anaerobic progression, becomes more a biologic marker of the status of the microbiologic environment induced by the anaerobic progression than the primary functioning pathogen. If therapy is

broadened significantly to encompass etiologic diversity and the anaerobic progress, that is, by the addition of cefoxitin, these figures become 90 and 80%, respectively.

Selection of antibiotic therapy for Stage II disease is one of the rare situations in which knowledge of the spectrum of organisms that can function in this type of polymicrobial infection is insufficient. Initial monomicrobial disease may be due to three entities that

Table 75.7 Therapeutic recommendations for acute salpingitis within a hospital setting

Regimen A
Cefotetan 2 g IV every 12 hours, or Cefoxitin 2 g IV every 6 hours PLUS Doxycycline 100 mg IV or p.o. every 12 hours
Regimen B
Clindamycin 900 mg IV every 8 hours PLUS Gentamicin loading dose IV or IM (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing may be substituted.
Alternative parenteral regimen
Limited data support the use of other parenteral regimens, but three regimens have undergone at least one clinical trial and have broad spectrum coverage.
Alternative parenteral regimens
Ofloxacin 400 mg IV every 12 hours PLUS Metronidazole 500 mg IV every 8 hours Ampicillin/sulbactam 3 g IV every 6 hours PLUS Doxycycline 100 mg orally or IV every 12 hours Ciprofloxacin 200 mg IV every 12 hours PLUS Doxycycline 100 mg IV or p.o. every 12 hours, PLUS Metronidazole 500 mg IV or p.o. every 8 hours

*Cefotetan does not have an anaerobic coverage total comparable to cefoxitin. The anaerobic coverage of selected second generation cephalosporins is why they haven't been supplanted by third generation cephalosporins, (ceftizoxime, cefotaxime, and ceftriaxone)

potentially influence antibiotic selection: *N. gonorrhoeae*, the PPNG, and *C. trachomatis*. Polymicrobial bacterial superinfection requires the traditional four-category coverage of the Gainesville Classification. The therapy of choice for Stage I or II disease is cefoxitin 2 g IV every 6 hours PLUS doxycycline 100 mg IV or pro, every 12 hours (Table 75.7).

Because of pain associated with infusion, doxycycline should be administered orally when possible, even when the patient is hospitalized. In the event that intravenous administration is warranted, use of lidocaine or other short-acting local anesthetic, heparin, or steroids with a steel needle or extension of the infusion time may reduce infusion problems. Parenteral therapy may be discontinued 24 hours after a patient shows clinical improvement, and oral therapy with doxycycline 100 mg 2 times a day should continue for a total of 14 days. The rationale for the antibiotic combination of cefoxitin and doxycycline is to achieve the best coverage for the maximal numbers of these seven categories (Table 75.8). Cefoxitin and doxycycline offset each other's relative deficiencies. The principal shortcoming of this drug combination is its inadequacy for enterococci.

If the presence of tubal occlusion or a TOC is suspected, the disease should be staged upward in terms of a presumptive Stage II to Stage III, and antibiotic therapy with penicillin, clindamycin, and an aminoglycoside (triple therapy) should be implemented. Once signs of peritoneal irritation have abated, ultrasonography should be performed to stage the disease accurately (peritoneal irritation precludes earlier use of ultrasonography because of the inability to fill the bladder). If ultrasonography reveals merely tubal occlusion, aminoglycoside therapy can be discontinued. If a tubo-ovarian complex is identified, aminoglycoside therapy is continued for a total of 72 hours.

Stage III—Suspected tubal occlusion or tubo-ovarian complex

In selected instances, the interstitial inflammation and secondary edema result in focal tubal occlusion at a proximal and distal part. The inflammatory exudate, denied access to the peritoneum and cul-de-sac or retrograde drainage into the endometrial cavity, exerts volumetric intraluminal pressure, thus increasing the local diameter of the fallopian tube. Prior structural damage with focal submucosal fibrosis predisposes to the evolution of this type of clinical presentation. The distinction between transitory tubal occlusion and TOA is determined by the permanency of the occlusions.

Stage III (tubal occlusion or a TOC) represents the anatomic progression of disease. The probability of preserving fallopian tube function is diminished. The major goal becomes the preservation of ovarian function by negating the need for surgical intervention. We use triple therapy (penicillin, clindamycin, and an aminoglycoside)

Table 75.8 Rational use of cefoxitin and doxycycline in acute salpingitis (Stage II)

Antibiotic	*Neisseria gonorrhoeae*	*Chlamydia trachomatis*	*Penicillinase-producing Neisseria gonorrhoeae*	*Categories of the Gainesville Classification*			
				I	*II*	*III*	*IV*
Doxycycline	+++–++++	++++	+–++[a]	++1/2	++1/2–+++ (75–85%	+–	++
Cefoxitin	+++–++++	–	+++–++++	+++	++1/2 (75–85%)	–	+++

Combined coverage	+++−++++	++++	+++−++++	+++	+++−+++[b] (85–90%)	+−	+++

+++=≥85% efficiency. ++++=≥94% efficiency.
[a]Effectiveness of doxycycline and cefoxitin limited to African strain of *Neisseria gonorrhoeae*.
[b]Effectiveness is additive for the penicillin-resistant *Bacteroidaceae* (Category II)

in this setting. Why the need for an aminoglycoside? In our experience when rupture has occurred, *Enterobacteriaceae* frequently are present. The therapy of Stage III is primarily a therapeutic assault on the anaerobic progression. Duration of aminoglycoside therapy rarely needs to exceed 72 hours. It is our policy to discontinue parenteral therapy 24 hours after rectification of monitored parameters.

A major advance in therapy of Stage III disease will be the use of percutaneous and transvaginal aspiration drainage under ultrasonographic guidance. Use of this technique in TOCs which remain tender after 48 hours lessens morbidity and shortens hospital stays.

Stage IV—Ruptured tubo-ovarian complex

In Stage IV, rupture of a TOC has occurred. The therapeutic goal for Stage IV disease is the preservation of life. The distinction between tubal and ovarian sites is predicated on the observation that occasional patients with tubal sites of rupture may respond to medical therapy. In these cases, closure of the site of rupture is probably provided by the mating of omentum or bowel to the site of rupture. When the infection directly involves the ovary, the probability of associated concomitant septic thrombophlebitis is markedly increased. Unless surgical intervention is implemented, mortality is the anticipated outcome for patients with a ruptured ovarian abscess. Therapy for Stage IV disease is surgical removal of the site of rupture under appropriate antibiotic coverage. Triple therapy (penicillin, clindamycin and an aminoglycoside) is administered to minimize or abort metastatic infectious complications. Definitive therapy involves the surgical removal of the diseased organ and effective peritoneal lavage. If an ovarian abscess is found at the time of surgery, care must be given to ruling out concomitant septic thrombophlebitis.

DURATION OF ANTIMICROBIAL THERAPY FOR ACUTE SALPINGITIS

What constitutes a good therapeutic response is a controversial issue. The duration of antibiotic therapy for acute salpingitis is not known. Determination of the length of antibiotic administration requires identification of therapeutic titration points. For many, including the CDC, organismal eradication, resolution of the signs and symptoms of disease within a four-day period, and non-progression to a TOC equated with a good therapeutic response. Once it was documented that—in the absence of complicating factors such as the use of an IUD, significant prior structural damage, or tubal ligation—monomicrobial disease had an anticipated therapeutic response (lysis of fever within 36 hours, disappearance of signs of peritoneal irritation and marked amelioration of deep

organ tenderness within 36 to 48 hours, and a WBC below 10000/mm^3 within 48 hours after the onset of therapy), the questions become how long does therapy need to be continued

Table 75.9 Omaha criteria for possible ambulatory care of acute gonococcal salpingitis

(1) Non-adolescent/non-nulligravida women
(2) Ability to demonstrate presence of Gram-negative intracellular diplococci on Gram stain of endocervix
(3) ESR less than 30 mm
(4) Absence of signs of peritoneal irritation (rebound tenderness)
(5) High probability of follow-up in 24–48 hours
(6) No prior history of documented salpingitis or chlamydial infection
(7) Absence of pregnancy

and which antibiotics should be utilized? One way to evaluate therapy is to use multiple parameters: patient's sense of well-being, serial WBCs, abdominal and pelvic physical findings, and temperature. This permits the establishment of an end-point for Stages II and III disease. The ESR should be followed in Stage III disease to decide on the duration of therapy. The ESR should be declining before the discontinuation of multiple drug therapy. Once the therapeutic end-points have been documented, our policy is to continue parenteral antimicrobial therapy for 24 hours and then discharge the patient to continue with oral medication.

Outpatient therapy for Stages I and II disease is that required to complete therapy for eradication of *C. trachomatis*. Our drug of choice is doxycycline. Five days of oral therapy is the upper limit of patient compliance that we can achieve in a primarily poorly educated, low socioeconomic population without again seeing the patient in the gynecologic clinic. Outpatient therapy of Stage III acute salpingitis involves the administration of metronidazole and doxycycline. The duration of doxycycline therapy is governed by the time of administration required to eradicate *C. trachomatis*. Duration of metronidazole therapy is based on the CRP or ESR changes.

The real answers as to appropriate antimicrobial therapy for each of the Gainesville stages of acute salpingitis and for corresponding duration of therapy ultimately need to be assessed longitudinally through detailed studies of subsequent fertility.

CRITERIA FOR THE SELECTION OF PATIENTS FOR AMBULATORY THERAPY OF ACUTE GONOCOCCAL SALPINGITIS

No firm criteria exist that delineate which patients with acute gonococcal salpingitis can be successfully managed on an outpatient basis and which patients would be best handled

by hospitalization. The following segment represents personal guidelines which govern selection of candidates for ambulatory therapy of acute salpingitis.

The criteria governing patient selection for ambulatory care of women with acute salpingitis are listed in Table 75.9.

Unless the issue of future fertility is not a consideration, first and foremost, my personal policy is to offer and counsel hospitalization for all women with acute gonococcal salpingitis. Even when all other ambulatory care criteria are met, hospitalization is most adamantly advocated for all adolescents and nulligravidas. Hospitalization should be used as an educational as well as a therapeutic vehicle.

Gram stain demonstration of Gram-negative intracellular diplococci in endocervical smear

Demonstration of Gram-negative intracellular diplococci correlates with 10^4 or greater cfu/ml of bacteria in the sample fluid. The visual demonstration of a high multiplicity of *N. gonorrhoeae* argues against significant alteration of the microbiological environment so as to favor the replication of Class II anaerobes which will in turn lead to the ultimate autoelimination of the gonococcus. The Gainesville studies of acute salpingitis documented that the demonstration of Gram-negative intracellular diplococci in smears from the endocervix was associated with a statistically significant increased probability that one was dealing with monoetiological bacterial disease.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate has been a valuable adjunctive laboratory aid. The ESR was used primarily in staging patients with significant peritoneal irritation in the interim prior to ultrasonographic evaluation. A value of 60 mm or greater correlated in a statistically significant manner with the probability of a tubal occlusion or TOC as demonstrated by ultrasonography. Most patients with acute gonococcal salpingitis tend to have ESRs in the 20s and low 30s. The use of ESR in chlamydia salpingitis is nearly worthless. Patients with laparoscopically documented TOCs may have normal ESRs.

The choice of an ESR of 30 mm as a demarcation point in deciding whether or not to hospitalize a patient is arbitrary, predicated on a desire to err on the side of patient welfare.

Prior or advanced disease presentations

The ‘therapeutic window’ (that interval in which effective antibiotic therapy against monoetiological disease due to *N. gonorrhoeae* will preclude alteration of fallopian tube structure and function) may be as short as 24 hours. Prior structural damage may, through the acceleration of the anaerobic progression as a consequence of adverse impact on local host defense mechanisms, reduce the time frame in which the therapeutic window functions. Based on theoretical considerations, hospitalization for all patients with disease beyond Stage I acute salpingitis is recommended. The issue of therapeutic window for *C. trachomatis* cannot be defined based on current experience or data.

Prior history of chlamydial infection

Since prior or concurrent structural damage to the fallopian tubes cannot be ruled out, asymptomatic or minimally symptomatic chlamydial infection, for management purposes, is deemed equivalent to prior salpingitis. Thirty-four percent of individuals with endocervical chlamydial infection will have the presence of lymphocytic-plasma cell infiltration in their endometrial biopsy. What percentage of these have concomitant fallopian tube involvement and whether the process identified by histology is due to *C. trachomatis* are issues for continued analysis.

Table 75.10 Ambulatory care for acute salpingitis

Only women with clinically documentable stage I disease, with the following exceptions:
Pregnant women
Teenaged women and girls
Any nulligravida female who desires future pregnancy
Any female who is unable to take oral medication or unable to be seen in follow-up

From Guidelines for PID, CID 2001:32(1 Jan)

Absence of peritoneal signs

Patients whose clinical findings go beyond the criteria of lower abdominal pain, cervical motion tenderness, adnexal tenderness and two or more of the minor diagnostic criteria and who have demonstrable rebound tenderness represent individuals with a more advanced stage of disease, in which the probability of polymicrobial superinfection is markedly augmented. The option for possible ambulatory therapy should be restricted to those patients with monoetiological disease due to *N. gonorrhoeae* or coinfection due to *N. gonorrhoeae* and *C. trachomatis*.

Pregnancy

When acute salpingitis occurs in a gravida, it does so within the first eight weeks of gestation. The pathogenesis of disease partially embraces the same mechanisms which result in superinfection. An exceedingly rare case may occur at twelve weeks gestation. Intrauterine disease places the pregnancy at risk. For maximum fetal support, hospitalization is strongly recommended. Despite effective maternal therapy, 30–40% of patients will abort either in association with maternal disease or within two to three weeks post-therapy.

In 2001, the International Infectious Disease Society published its recommendation for ambulatory care (Table 75.10).

The PID Evaluation and Clinical Health (PEACH) randomized trial is the most recent attempt to compare the efficacy of outpatient vs. inpatient therapy for ‘PID’. Unfortunately the study was fundamentally flawed by reliance on the CDC’s definition of PID. The inclusion of a large number of patients who were not documented to have gonococcal or chlamydial disease

Table 75.11 1998 CDC therapeutic recommendations for ambulatory therapy of acute salpingitis

Regimen A
Either ceftriaxone 250 mg IM once, or Cefoxitin 2 g IM plus probenecid, 1 g orally in a single dose concurrently once, or Other parenteral third-generation cephalosporin (e.g. ceftizoxime, cefotaxime), PLUS Doxycycline 100 mg orally bid for 14 days, PLUS Metronidazole 500 mg PO tid for 7 days
Regimen B
Ofloxacin 400 mg orally bid for 14 days PLUS Metronidazole 500 mg orally bid for 14 days
Alternative oral regimens
Amoxicillin/clavulanic acid 250/125 mg orally every day for 14 days PLUS Doxycycline 100 mg orally every 12 hours for 14 days

diluted the validity of conclusions which centered on the occurrence of long-term sequelae.

AMBULATORY CARE MANAGEMENT

Patients receiving oral therapy should show substantial clinical improvement (e.g. defervescence, reduction in direct or rebound abdominal tenderness and reduction in uterine, adnexal, and cervical motion tenderness) within 36 hours of initiation of therapy (Table 75.11).

If the provider elects to prescribe oral or parenteral outpatient therapy, follow-up examination should be performed within 36–48 hours using the criteria for clinical improvement previously described.

Because of the risk for persistent infection, particularly with *C. trachomatis*, patients should have a microbiologic re-examination 7–10 days after completing therapy. Some experts also recommend rescreening for *C. trachomatis* and *N. gonorrhoeae* 4–6 weeks after completing therapy If using polymerase chain reaction or ligase chain reaction to document test of cure, rescreening should be delayed one month following completion of therapy.

MANAGEMENT OF SEX PARTNERS

Evaluation and treatment of sex partners of women who have PID is imperative because of the risk for re-infection and the high likelihood of urethral gonococcal or chlamydial infection of the partner.

Sex partners should be treated empirically with regimens effective against both of these infections.

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Ruptured tubo-ovarian abscess

ANATOMICAL CONSIDERATIONS

In the majority of instances the term tubo-ovarian abscess (TOA) is a misnomer. Abscess indicates the collection of purulent exudate within a newly created tissue space. The majority of so-called tubo-ovarian 'abscesses' are nothing more than collections of pus within an anatomically distinct space created by two point closure. A superior term to 'abscess' is that of a tubo-ovarian complex (TOC). While the ovaries are frequently involved in the resultant inflammatory mass, the ovarian capsule is an effective barrier to parenchymal involvement. Consequently, a perioophoritis rather than intraparenchymal disease occurs. If a fresh corpus hemorrhagica is present to provide the critical portal of infection, a true ovarian abscess may develop.

Isolated ovarian abscesses can occur. They usually evolve in association with vaginal hysterectomy or with ovarian biopsies (particularly if done concomitantly with an incidental appendectomy or an invasive procedure on the gastrointestinal tract). Any break in the ovarian capsule introduces the potential for contamination and subsequent development of an abscess. Isolated ovarian abscesses are far more dangerous than an ovarian abscess within a TOC. Because of its anatomical positioning, when rupture occurs from an ovarian abscess, spillage tends to be into the peritoneal rather than the pelvic cavity. Significant spillage into the peritoneal cavity is often associated with clinically overt septic shock. In contrast, TOCs tend to be bound down into the pelvis. The pelvis does not have the same absorptive capacity as does the peritoneal cavity and consequently the induction of hypotension, disseminated intravascular coagulopathy, etc. are far less frequent events for patients with ruptured TOCs. Any time the ovary is the site of abscess formation, the potential for subsequent development of septic thrombophlebitis is present. The induction of unrecognized thrombophlebitis and its metastatic complications secondary to septic thromboemboli can be the deciding factors determining outcome in a critically ill patient. A TOC must be distinguished from a pelvic abscess. The latter may co-exist with a TOC. The most common pelvic abscess is that which occurs in and around the adnexa where one wall is the broad ligament and the other, the adnexa. Another type is that where the anterior abdominal wall and the posterior wall are the bowel and omentum. The large pelvic abscesses occur in the posterior cul-de-sac and rarely in the anterior cul-de-sac.

PATHOGENESIS OF RUPTURED TUBO-OVARIAN ABSCESS

A significant number of etiological agents is capable of altering the anatomy of the fallopian tubes, ovaries and uterus; yet the events which combine to produce a ruptured TOC are basically limited to endogenous anaerobic bacteria. *Mycobacterium tuberculosis*, *Coccidioides immitis*, and schistosoma can all produce significant disease involving the fallopian tubes, but not abscess formation. *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, while the catalytic agents for the induction of disease, do not *per se* cause abscess formation. The gonococcus, by virtue of its replication, alters the microbiological environment and, in so doing, induces the anaerobic progression. *Neisseria gonorrhoeae* cannot replicate or survive in the intra-abscess environment. Superinfecting anaerobic bacteria in conjunction with *Enterobacteriaceae* are the most frequent microbial combinations associated with rupture of a previously anatomically altered fallopian tube. There is a tendency for rupture of a TOC to occur on the left side. The close anatomic relationship between the descending sigmoid colon and the adnexa on the left side has been cited as being etiologically significant. Although the fallopian tube is commonly regarded as the prime site of rupture, the involvement of the ovarian parenchyma is the most important factor which selects for rupture. The fimbriated end of the tube becomes attached to the ovarian cortex, and infected material within the tube may gain access to the ovary either through the site of follicular rupture or, under rare conditions, by direct penetration of the ovarian tunic. An ovarian abscess is a true abscess and not an entrapped loculation of purulent material. Pedowitz and Bloomfield, in their report of 44 cases of ruptured TOA, found that in 28 cases the site of rupture was the ovary. Once an ovarian abscess develops, lack of an overlapping distensible muscularis mucosae renders the ovary more vulnerable than adnexal structures to rupture. With appropriate antibiotic therapy, the interstitial and submucosal edema elicited recedes, permitting effective drainage of the loculated purulent material either through the uterus or into the pelvic cavity. Whether resolution, entrapment, or rupture ensues is determined by the effectiveness of antimicrobial therapy and the ability of the muscularis to accommodate the engendered intraluminal pressure.

While the sexually transmitted diseases (STDs) are the prime disease entity capable of producing fallopian tube complexes which rupture, they do not represent the sole mechanism. A chronic anaerobic endometritis (CAE) may develop as a consequence of prolonged use of an intrauterine contraceptive device (IUD). If superimposition of a STD or myometrial penetration occurs, the CAE appears to accelerate the anaerobic progression. If the device has mechanically penetrated the endometrium, it will effectively circumvent the uterine barrier to anaerobic infection. An important distinction between these two mechanisms is that in the case of STD-induced disease more bilateral disease is likely to develop, whereas with myometrial penetration there is usually almost complete sparing of the contralateral fallopian tube.

DEMOGRAPHIC CHARACTERISTICS OF HIGH-RISK PATIENTS

Patients who experience rupture of a TOC exhibit two distinct demographic profiles.

One group is usually from a disadvantaged background. A TOC which ruptures tends to occur in older women, in the third or fourth decade. Frequently, there is an antecedent history of acute inflammatory disease or documented secondary infertility.

The second group tends to have a history of fertility which has been interrupting prolonged use of the IUD. Not infrequently, a prior history of foul-smelling intramenstrual discharges or menstrual irregularities can be elicited. The prodromal signs and symptoms leading up to rupture tend to be more like those of subacute disease in contrast to the relatively acute onset observed when a STD is the principal catalyst.

CLINICAL MANIFESTATIONS OF PATIENTS WITH RUPTURED TOC

There are two basic categories for patients with ruptured TOCs. They are either hemodynamically compromised or hemodynamically stable.

Hemodynamically compromised patients

Those individuals who have had significant peritoneal spillage will present with evidence of septic shock or of an intra-abdominal catastrophe. The recognition of an adnexal mass is instrumental in formulating the differential diagnosis.

Rupture is usually heralded by a sudden, severe thrust of pain at the site of rupture. The predilection of rupture for the left side may be significant in the differential diagnosis of a woman complaining of acute abdominal pain. The clinical pattern depends primarily on the degree of rupture sustained. Although the predominant pain pattern involves the lower abdomen with localization to the rupture site, it may occasionally be that of upper abdominal pain, especially marked in the right upper quadrant. Spread of exudate up the colonic gutters and under the liver and diaphragm may so accentuate the signs and symptoms in the upper abdomen as to mask the clinical features of pelvic disease. However, pelvic pain and tenderness are almost always present. With rupture of a TOA in a bedridden patient, it is not uncommon for the patient to experience shoulder pain indicative of diaphragmatic irritation. If a concomitant pelvic abscess is present, diarrhea is a prominent symptom. Once a generalized peritonitis has developed, bowel function ceases. For those patients who present with shock, the onset of pain is frequently followed by chills, less often by vomiting, in conjunction with the signs of generalized peritonitis and progressive vasomotor collapse. The degree of rupture and peritoneal cavity involvement determine the rapidity with which shock becomes manifest. Shock grossly correlates with the amount of inflammatory exudate liberated into the intraperitoneal cavity.

In contrast to most inflammatory conditions, the temperature is so variable as to be of little or no diagnostic significance. Not infrequently, patients with ruptured TOAs have temperatures between 38 and 38.6ºC. A common clinical finding in these patients is a tachycardia far beyond that expected with the temperature observed. Leukocytosis in excess of 20000 is characteristic; however, patients have been seen with marked leukopenia (which is usually a poor prognostic indicator).

Hemodynamically stable patients

More commonly, the patient presents with signs and symptoms which are almost indistinguishable from patients with ruptured TOC.

The major diagnostic dilemma is distinguishing the ruptured from the unruptured TOC (Tables 76.1 and 76.2). Most patients with unruptured TOA respond within 72 hours to aggressive systemic administration of antibiotics and fluid replacement. The development of rectal tenesmus, diarrhea, progressive tachycardia, prolonged fever, or the persistence of peritoneal signs should suggest the possibility of a ruptured TOA. Such patients require operative intervention. Even in the acute phase of abscess, aggressive surgical therapy has been done in a controlled situation without undue serious difficulties in the postoperative period. In many cases of ruptured unilateral TOD associated with prolonged IUD use, there appears to be a prodromal syndrome before abscess formation during which the patient complains of vague lower abdominal pain, pelvic tenderness, and dyspareunia. While most patients are symptomatic weeks to months prior to the detection of an adnexal mass, a few may have a rather rapid course, which if not aggressively treated may result in perforation, peritonitis and death. This sequence is particularly true when *Actinomyces israelii* is the predominant anaerobic bacterium.

BACTERIOLOGY

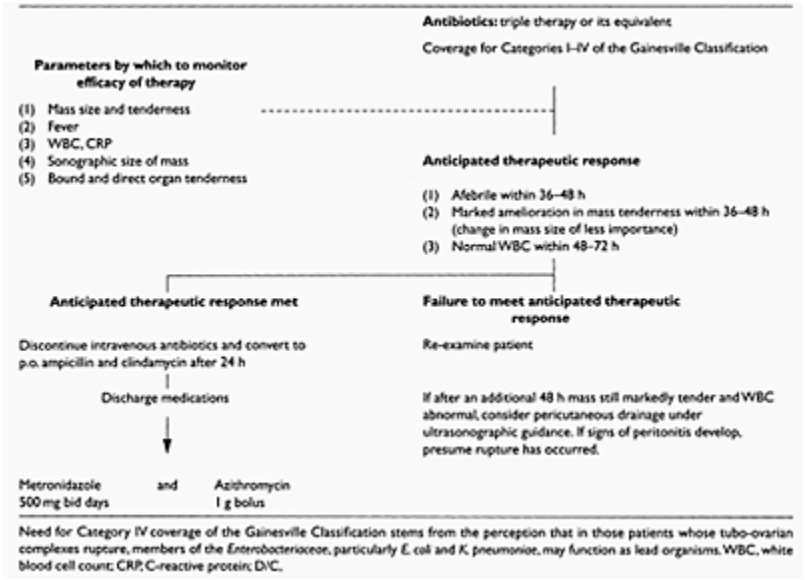
Although it is generally conceded that infection with *N. gonorrhoeae* is of overwhelming importance in the initial alterations of tubal and ovarian architecture, cultures of a ruptured TOA rarely yield the gonococcus. The conditions of abscess are not conducive to multiplication of *N. gonorrhoeae*. The principal bacteria isolated include members of the *Enterobacteriaceae,* coagulasepositive *Staphylococcus aureus,* the peptostreptococci, enterococci and the *Bacteroidaceae*. The incidence of recoveries of *Enterobacteriaceae,* particularly *Escherichia coli* and *Klebsiella pneumoniae,* is disproportionately high when compared to the incidence of their recovery from the cul-de-sac of women with acute salpingitis. The presence of *Enterobacteriaceae* is postulated to be one of the catalytic ingredients necessary for rupture to occur. When rupture occurs in the setting of prolonged IUD usage and the associate CAE, the presence of *A. israelii* and the *Bacteroidaceae* in the polymicrobial anaerobic infection appear to be factors selecting for this complication.

RUPTURED TUBO-OVARIAN COMPLEX IN PREGNANCY

The development of a TOC in a pregnant woman can reputedly evolve through four mechanisms:

(1) formation following abortion or attempted interruption of pregnancy;
(2) intrapartum formation due to acute salpingitis in the first 8–12 weeks of gestation;
(3) pre-existent tubo-ovarian salpingitis antedating pregnancy wherein disease was localized primarily to one of the adnexa and developed prior to the establishment of conception; and
(4) unilateral ovarian abscess unassociated with tubal involvement.

Table 76.1 Management of tubo-ovarian complexes



The pathogenesis of TOAs in the context of pregnancy has been an area of broad speculation. Friedman and Bobrow, in their review of pelvic inflammatory disease (PID) in pregnancy, remarked on the propensity of salpingitis to occur during the first half of pregnancy, whereas ovarian and TOAs were distributed equally through pregnancy. This observation coupled with the barrier to ascending infection constituted by the cervical plug of the cervix and intact fetal membranes has fostered the concept that some, if not most abscesses have a different pathogenesis than that associated with gonococcal infection in the non-pregnant female.

Once pregnancy is established, ascending infection due to *N. gonorrhoeae* is a rare event and after the first 8 to 16 weeks of gestation virtually never occurs. Access to the endometrial cavity in this latter time frame may occur because of continued ovulation.

Ovulation induces changes in the endocervical mucus which facilitate bacterial and sperm penetration. The progressively diminishing incidence of superinfection and acute gonococcal salpingitis with time indicates that this phenomenon is time limited. Development of a TOC in association with gonococcal infection is due primarily to polymicrobial superinfection. *N. gonorrhoeae*, through its impact on the local microbiological environment, permits Class II and III anaerobic bacteria to govern the subsequent course of disease. Reported cases of TOCs in pregnancy are remarkedly few. The earliest case in the English literature was reported in 1869. A ruptured TOC was found at the

Table 76.2 Sequence management of ruptured tubo-ovarian complex

Diagnostic findings
(1) Demonstration of a pelvic mass (either by bimanual examination or sonography)
(2) Elevated ESR (>60 mm)
(3) Tachycardia out of proportion to fever
(4) Signs of pelvic or abdominal peritonitis
(5) Pus demonstrable on culdocentesis
(6) Progression of disease despite triple therapy
Management sequence
(1) Central venous monitor—preferably utilizing wedge pressure
(2) Aggressive IV therapy to re-expand contracted intravascular compartment (may require RBCs) and correct electrolyte imbalances
(3) Antibiotics—triple therapy or triple therapy equivalent
(4) Cross match and type
(5) Vasogastric suction for decompression and insertion of urinary catheters
Laparotomy
Magnitude of operative procedure directed by the findings at the time of surgery Drainage of the lower pelvis using soft rubber clamp drains through vaginal vault, plus abdominal drains is advocated

ESR, erythrocyte sedimentation rate; RBCs, red blood cells

autopsy of a pregnant woman who died on the tenth postpartum day of a generalized peritonitis. Subsequent cases have been sporadically reported. Jafari *et al.* reviewed 19 cases that were documented by laparoscopy. The identification of disease was scattered

throughout the gestational period. Six were diagnosed in the first trimester, eight in the second, and five in the third. Only two TOCs were found at term. Of these 19 cases, in only one instance was the diagnosis made preoperatively.

Dudley *et al.*, in reviewing the literature, noted certain factors peculiar to ovarian abscesses and TOCs in pregnancy. All previous cases of TOCs were unilateral and more importantly all occurred on the right side. In all of the cases, the opposite adnexa was found to be normal. This observation has been cited as evidence that the etiology of TOC in pregnancy is different than in the absence of pregnancy

RUPTURED TUBO-OVARIAN ABSCESS AFTER MENOPAUSE

Tubo-ovarian abscesses are considered a problem of women of childbearing age. When they occur in postmenopausal women they present formidable problems in both diagnosis and therapy. In contradistinction to the history in premenopausal women, a prior history of salpingitis is uncommon. The most frequent presenting symptom is postmenopausal bleeding or lower abdominal pain. As is characteristic of other infectious disease processes in older patients, systemic signs of infectious morbidity are often depressed. Only 50–60% of patients will have concomitant fever and leukocytosis. Not infrequently, individuals show few or no signs and come to laparotomy without invoking any preoperative suspicion of the possibility of a ruptured TOA.

The pathogenesis of this entity involves multiple factors and may be distinct from that in the premenopausal woman. A significant percentage of cases have either primary disease in the gastrointestinal tract with apparent secondary involvement of the female genital tract or an associated genital tract malignancy: invasive carcinoma of the cervix or adenocarcinoma of the fallopian tubes. At laparotomy the finding of bilateral TOA is more common than unilateral disease. The bacteriology of this disease entity is poorly defined. Most laboratories do not resort to the use of appropriate anaerobic technology. Aerobically, the most significant organisms isolated are members of the *Enterobacteriaceae* (*E. coli, K. pneumoniae*, etc). The most common bacteria isolated from the intravascular compartment have been the *Bacteroidaceae* and the peptostreptococci.

The patients in whom rupture has occurred differ by virtue of evidence of infectious morbidity. Almost invariably they present with fever, lower abdominal pain, and tachycardia. Abdominal distention associated with decreased bowel sounds ensues. Less frequent is the development of rebound tenderness.

DIAGNOSIS

The diagnosis of a TOC in pregnancy is seldom made prior to actual rupture; even then, inconsistencies of the signs of peritonitis in pregnancy render the diagnosis difficult. The clinical presentation varies significantly. Ultimately, however, the patient manifests the signs of peritoneal irritation or overt peritonitis followed by impending vasomotor collapse. The differential diagnosis is that which is classic for pregnancy, namely, appendicitis, ectopic pregnancy, hemorrhagic pancreatitis, and torsion and infarction of

an ovarian mass (e.g. a dermoid cyst). The only clinical clue that points to the probability of a ruptured TOC in pregnancy is documentation of PID prior to the establishment of pregnancy. Augmented technology achieved through ultrasonography and computerized axial tomography (CT scan) has impacted primarily on the ability to make the diagnosis of TOC rather than that of a rupture. Spirtes *et al.* have demonstrated that over 50% of cases with TOA will have significant fluid collections in the cul-de-sac. Its presence may not correlate with the apparent severity of disease. When bilateral TOCs are present, they may fill the pelvis and imperceptibly blend with the uterus. The concomitant presence of a significant amount of fluid in the culde-sac of a patient with a TOC and slowly resolving physical findings should bias clinical thought to the possibility that rupture has occurred. The demonstration of an abscess within the ovary is a mandate for operative intervention. Computerized axial tomography in the series reported by Knochel *et al.* is the more accurate of the two modalities and has better predictive value. The correlation between anatomical findings at surgery and diagnostic CT scan was 96% compared to 90% with ultrasonography. However, because of the cost differential and the need to respect the intents of DRG (Diagnosis-Related Groups), ultrasonography is preferentially used.

The presumptive diagnosis of ruptured TOC is made by clinical evaluation. Basically, you have a patient who has clinical findings which are inconsistent with anatomically limited disease and which have persisted despite appropriate medical therapy (Table 76.1). Under careful questioning, about a third of the cases of ruptured TOCs will give a characteristic history. Initial pain is in the lower quadrant and is crampy in nature. A sudden exacerbation and/or change in the character of the lower abdominal pain will then occur. The pain not infrequently gets transiently better only to return within hours. At this time the pain becomes more constant and is sharp rather than colicky in character. The magnitude of temperature elevation does not tend to mirror the severity of disease. The white blood cell count (WBC) is usually elevated and shifted to the left. Almost invariably the erythrocyte sedimentation rate (ESR) is above 60 mm/h when disease is associated with or initiated by *N. gonorrhoeae*. The most significant clinical clue is the presence of four quadrant abdominal tenderness. Three quadrant rebound tenderness can develop when the Curtis-FitzHugh variant of gonococcal or chlamydial peritonitis is present, but rarely does it involve all four quadrants. The presence of four quadrant tenderness is a clinical red light.

In many instances, the diagnosis of rupture is in dispute. When dealing with a medically stable patient, it is not inappropriate to treat such an individual with triple therapy and monitor closely the titration points. Patients with both ruptured and unruptured TOCs will initially respond to triple therapy or its equivalent. The persistence of peritoneal signs, a WBC>15000, tachycardia inappropriate for temperature beyond four days in association with persistent mass tenderness should reinforce the concept that one may be dealing with a ruptured TOC which is partially sealed by an overlay of bowel and omentum.

MANAGEMENT OF A RUPTURED TUBO-OVARIAN COMPLEX

Therapy requires an understanding of the potential lethal complications which can ensue (Table 76.2). Women with rupture can die due to:

(1) adult respiratory distress syndrome (ARDS);
(2) septic shock;
(3) inappropriate management of intravascular volume; and
(4) septic thrombophlebitis and metastatic complications.

Physicians must anticipate that their patient may:

(1) become hypovolemic;
(2) develop ARDS;
(3) exhibit some evidence of acute tubular necrosis;
(4) develop local (loop-to-loop or subphrenic) or distant (pulmonary) abscesses; or
(5) develop wound infection and/or wound dehiscence.

The prerequisites for a good outcome are:

(1) a good anesthesiologist;
(2) use of a Swan-Ganz catheter;
(3) aggressive antibiotic therapy;
(4) therapy of ARDS;
(5) surgical removal of diseased organ;
(6) retention sutures; and
(7) secondary closure.

Swan-Ganz catheter

An anesthesiologist should be used for the placement of a Swan-Ganz catheter. This permits re-expansion of the intravascular volume by using the pulmonary artery wedge pressure (PAWP) as the guiding parameter.

Antibiotics

The patient is placed on a fourth generation semisynthetic penicillin and metronidazole. This combination gives excellent I, II and III coverage in terms of the Gainesville Classification. The Category IV weakness is covered by the bolus aminoglycoside therapy which is maintained at therapeutic levels by the induced alterations in renal function. The appropriate dosage of netilmicin (adjusted for body weight) is given and thereafter the drug is usually stopped. Continued use of an aminoglycoside is contingent upon assessment of the patient's renal status.

Some form of tubular necrosis is to be anticipated and hence the necessity to limit the prolonged administration of nephrotoxic drugs. Netilmicin and tobramycin are the least nephrotoxic of the aminoglycosides.

Adult respiratory distress syndrome

ARDS is an extreme form of non-cardiogenic pulmonary edema associated with alveolar-capillary damage. Clinical features include acute respiratory distress, dyspnea and tachypnea, severe hypoxemia refractory to oxygen therapy, and diffuse bilateral pulmonary infiltrates. Pulmonary capillary hydrostatic pressure is usually normal. Filling or closure of alveoli leads to reduced functional residual capacity, decreased pulmonary compliance, and intrapulmonary right-to-left shunting. Shock or sepsis, functioning separately or in consort, can cause ARDS, but the processes leading to the alveolar permeability defect are not understood. Therefore, therapy remains non-specific and supportive. Treatment includes positive end-expiratory pressure, careful fluid management, steroid therapy and adequate nutrition. Unfortunately, even with the most sophisticated intensive care, the mortality of ARDS is greater than 50%.

Surgical intervention

Increased morbidity and mortality are directly related to the degree of procrastination prior to operative procedure. Many clinicians consider 12 hours the upper limit of safety, emphasizing the importance of close observation, early diagnosis, and prompt surgical intervention. Next to the general condition of the patient, the time interval before surgery takes prognostic precedence over all other factors. In the series reported by Lardaro, only 1 of the 7 patients brought to surgical repair within 12 hours after rupture died, whereas 7 of the 12 patients operated on after 12 hours died. In general, if surgical treatment is performed within the first 12 hours, 70% of patients recover and 30% die. If surgery is performed after 48 hours, 20% recover and 80% die. Death approaches 100% if patients do not have the abscess removed.

The surgical procedure depends partly on the patient's clinical status. The procedure of choice is hysterectomy and bilateral salpingo-oophorectomy. Since the most difficult part of the procedure is mobilization of the adnexa from the uterus prior to their removal, the uterus can be extirpated with relative ease without excessive prolongation of the operation. If the patient is premoribund at the time of operative intervention, simple salpingo-oophorectomy should be performed.

It is important to explore the entire abdomen and to search out purulent loculations between loops of bowel and beneath the diaphragm. Copious irrigation of the entire abdomen with physiologic saline solution containing a potassium supplement is mandatory.

When possible, it is valuable to examine the pelvic veins carefully in all cases of TOA for suppurative pelvic thrombophlebitis due to *Bacteroides fragilis* or the anaerobic streptococci. Unless extensive, this complication is best treated with anticoagulants.

The possibility of preserving ovarian function should be explored; however, when a limited procedure is done, additional surgical treatment is not infrequently required. The effects of previous laparotomy and generalized peritonitis render such an operative procedure difficult, if not potentially hazardous.

In the total hysterectomy, peritonealization is often impossible; the vaginal vault is left open except for the hemostatic angle sutures. If subtotal hysterectomy is done, drainage can be achieved by splitting the cervix or by entering the vagina through the cul-de-sac. In most patients adequate drainage of the peritoneal cavity cannot be achieved. In general, no drain is left in the place of the vaginal cuff.

Wound closure

Closure of the peritoneum and fascial layers of the abdominal wall is best achieved with Tom Jones wire sutures and leaving the skin and subcutaneous area open, to be closed at a later date (Table 76.3). It should be noted that surgical rupture of a large ovarian abscess during the operation is relatively benign compared with rupture within the enclosed abdomen. The impact of a good diagnosis can be negated by an inadequate surgical exposure. A ruptured TOC should never be handled through a vertical incision. Be sure that the vertical incision extends sufficiently above the umbilicus to permit exploration of bowel and upper abdomen. Since anatomical relationships are often obscured or distorted, the operating physician must be experienced. The extent of surgery is that which is required to save an individual's life. When dealing with unilateral disease, if possible, residual ovarian function should be preserved.

The prior presence of generalized peritonitis and ileus negates any consideration of primary closure. It is best to use a permanent suture such as prolene or wire in the Smead-Jones fashion closing the perineum muscle and fascia in one layer and then leaving the subcutaneous tissue and skin open. This can usually be closed in four or five days or it can be left to granulate, but closing the subcutaneous tissue in the skin almost always results in a wound infection and leaving it open to be closed by secondary intention almost always results in healing without wound infection.

No one wants to deal with a major wound dehiscence in a previously severely stressed individual. Secondary closure is an important surgical adjunct. What we specifically recommend is summarized in Table 76.3.

LIGNEOUS CELLULITIS

This indolent cellulitis is another complication of chronic and repeated pelvic infections. Bacteriologic studies in terms of causative agents and pathogenesis are poorly delineated at the present time.

Symptoms are non-specific; postoperatively or posttherapy the patient may complain of fatigue, anorexia, vague pelvic discomfort, and/or weight loss. She may or may not be febrile. Not infrequently, abnormal or prolonged uterine bleeding may be the main reason the patient seeks medical care.

Bimanual examination reveals fixation of the pelvis. The pelvic floor has a characteristic woody-hard, smooth texture. It is not difficult to comprehend how the physician may misdiagnose the lesion as pelvic cancer. Biopsy of the endometrium and cervix reveals extensive inflammatory debris, and chronic infection rather than cancer. The WBC may be elevated but usually is normal. The patient is frequently anemic, with a hemoglobin level of 10 g or less. The ESR, a useful indicator of response to therapy, is elevated.

Once the diagnosis is made, the patient should be hospitalized, treated initially with antibiotics having Category I and II designation, and kept at bed rest.

Table 76.3 Management of the contaminated wound associated with ruptured tubo-ovarian abscess

(1) Close the fascia and peritoneum but leave the subcutaneous tissue and cutis open.

(2) Pack with moist gauze 4–5 times/day.

(3) Close secondarily on the 5th-6th day; prior to closing the wound, scrape both surfaces of the granulation tissue so that they ooze.
If one attempts to oppose two surfaces composed of granulation tissue by secondary closure, infrequently a serosoma forms.

Attention should be given to nutrition. Some clinicians have advocated simultaneous administration of cortisone or other anti-inflammatory agents with the antibiotic in order to speed resolution of the inflammatory process. However, this is rarely necessary.

When the patient's temperature has returned to normal and she is eating well, she may be discharged from the hospital with instructions to continue treatment at home by resting, adhering to a well-balanced diet, and taking an appropriate antibiotic.

Within 6–12 weeks, the cellulitis should clear. When the pelvic examination is normal, the patient should have a hysterectomy and bilateral salpingo-oophorectomy. Some patients with ligneous cellulitis develop septic pelvic thrombophlebitis heralded by spiking temperature, shaking chills, and (sometimes) pelvic or abdominal pain. Intravenous administration of heparin and more aggressive antibiotic therapy should be instituted.

OVARIAN ABSCESS

Ovarian abscess is a distinct clinical entity which should not be confused with TOA. These disease entities differ significantly both in their pathogenesis and in the clinical circumstances under which they occur. The overriding distinction is that TOA develops from a naturally occurring disease process, whereas isolated bacterial ovarian abscess is almost always an iatrogenic phenomenon.

Pathogenesis

The epithelial covering of the ovary exhibits a remarkable degree of resistance to bacterial penetration and involvement of the underlying stroma. What is required for bacterial penetration is either:

(1) a natural disruption of the ovarian surface epithelium and the subsequent creation of a new tissue space (as might be constituted by a hemorrhagic corpusluteum cyst);
(2) intentional or unintentional surgical incision into the ovarian parenchyma, subsequent hematoma formation, and bacterial contamination during a surgical procedure; or
(3) hematogenous seeding of a hemorrhagic corpus luteum cyst.

Most commonly, an ovarian abscess occurs after rupture of a follicular ovarian cyst with subsequent seeding of bacteria into the stigmata or colonization of the ovarian stroma. The onset of an ovarian abscess is insidious and usually presents as pain and low-grade fever with acute peritonitis occurring from 1 week to 6 months following initial contamination.

The suturing of the ovarian pedicle to the angle of the vaginal cuff places the adnexa in close proximity to any area containing devitalized tissue, which in turn is in contact with the vaginal flora (Figure 76.1). The surgical alteration of the natural barriers to infection permits penetration by the more aggressive bacterial organisms. In those circumstances in which a surgical procedure produces significant tissue damage, this process selects for a specific group of pathogens by creating an environment conducive to anaerobic growth. The pathogens cultured from an ovarian abscess are almost invariably those indigenous to the patient's own flora.

Natural history of the disease

Bacteria capable of septicemic disease from the gastrointestinal tract on occasion may seed a recently ruptured follicular site and create a metastatic abscess. Non-typhoidal salmonella have been recovered from an ovarian abscesses.

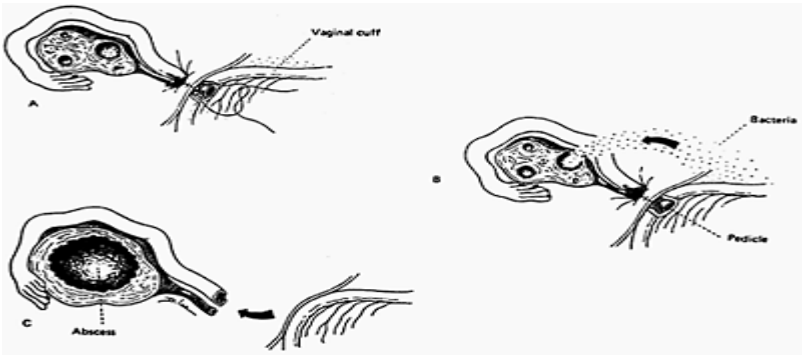


Figure 76.1 Proposed mechanism for development of an ovarian abscess after vaginal hysterectomy. A. The proximity of adnexal structures to the vaginal cuff following vaginal hysterectomy is shown. B. Postoperative ovulation estroma of the ovary to bacterial invasion from the infected vaginal cuff. C. Disintegration of the suture holding the pedicle to the vaginal cuff permits retraction of the adnexal abscess high into the pelvis (Ledger W *et al. Surg Gynecol Obstet* 1969; 129:973)

Ovarian abscess is primarily a disease of women of childbearing age. Some operative procedure precedes the establishment of infection; the great majority of cases occur following vaginal or gastrointestinal surgical procedures. Willison and Black note that the majority of their patients were in the secretory phase of the menstrual cycle and implied that the hemorrhagic corpus luteum cyst acted as the portal of infection for the ovary. However, this contention was not later substantiated by Ledger *et al.,* in whose study only 5 of the 17 patients with isolated ovarian abscess were known to be in the luteal phase. In the author's experience, patients with an isolated ovarian abscess have had either hemorrhagic corpus luteum cysts at the time of surgery or surgical penetration of the ovarian surface.

The interval between initial operative intervention and clinical manifestations of disease varies considerably, depending on:

(1) the dose of the bacterial inoculum;
(2) whether infection was due to direct contamination at the time of operation or to spread through devitalized tissue to a new tissue space; and
(3) the type of bacterium and its relative virulence.

In the characteristic case, the patient becomes febrile postoperatively. There may be an initial clinical response to antibiotics; however, it is usually transient, the patient again becoming septic (often before the termination of antibiotic therapy). It is not uncommon for there to be a prolonged delay of 6–45 days between operative procedure and clinical manifestation of abscess. In at least one instance 133 days elapsed between the two events. Bacteriologic analysis commonly reveals a single pathogen. In approximately one-third of the cases, two or more genera of bacteria have been isolated. The principal pathogens are the obligatory anaerobes, and in particular *B. fragilis* and the peptostreptococci.

Once abscess formation is well established, the patient develops the characteristic hectic spiking temperature curve. The WBC count is often in excess of 20000. Septicemia, clinically manifested by shaking chills, may occur and is often indicative of ovarian vein thrombophlebitis.

Therapy

The long interval between initial seeding of the ovary and clinical recognition of disease is often of sufficient duration to permit disintegration of the sutures holding the ovarian pedicle to the vaginal cuff, thus allowing retraction of the adnexal mass into the pelvis. When the ovarian pedicle still adheres to the vaginal cuff, the abscess may dissect through adjacent tissue and drain through the vaginal vault. However, when a sufficient interval occurs to permit retraction of the adnexal mass into the pelvis or when abscess has formed secondary to surgical disruption of the ovarian capsules at the time of elective appendectomy and the site of abscess is high in the pelvis, it is unlikely that such an abscess is amenable to simple surgical drainage.

Conservative management runs the risk of intraperitoneal abscess rupture. If this occurs, it is associated with high mortality (comparable to that seen with ruptured TOA). The treatment of ovarian abscess is abdominal excision within hours following institution of antibiotic therapy. Antibiotic therapy should be directed primarily against anaerobic

organisms. Large doses of penicillin in conjunction with metronidazole or clindamycin and tobramycin are deemed suitable combinations. Antibiotics are primarily administered to prevent systemic or metastatic complications. The definitive therapy of ovarian abscess is surgical, not medical.

OVARIAN ABSCESS FOLLOWING THERAPEUTIC INSEMINATION

Serious bacterial infections associated with therapeutic insemination are rare. Sable *et al.* reported the first case of a rupture TOA following intrauterine insemination. Kolb *et al.* have described a case of ovarian abscess following intrauterine insemination with the husband's semen. The patient became symptomatic within five days of insemination. Despite treatment with triple antibiotics, an oophorectomy was required. Violation of the natural cervical barrier which occurs with therapeutic insemination can, in rare instances, theoretically place the patient at increased risk for infectious morbidity.

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77
Pelvic abscess

James W.Daly, MD

The pelvic abscess may have a multiplicity of etiologies. While most pelvic abscesses are complications of sexually transmitted diseases (STDs), they may also be due to complications of pregnancy, chronic anaerobic endometritis associated with prolonged intrauterine device (IUD) usage, ruptured appendix, diverticulitis, or endomyometritis. A certain number of pelvic abscesses will be due to primary operations in the pelvis or in the upper abdomen. The discussion here focuses on those pelvic abscesses which are the consequences of STDs or pelvic surgery.

BACTERIOLOGY

Neisseria gonorrhoeae and/or *Chlamydia trachomatis* are the prime initiators of disease which ultimately produce a pelvic abscess; however, cultures of a pelvic abscess rarely yield these organisms. The principal bacteria isolated from pelvic abscesses include members of the *Enterobacteriaceae*, the peptostreptococci, the peptococci and the *Bacteroidaceae*. The high incidence of negative cultures or 'sterile abscess' primarily tends to reflect the lack of skill in taking anaerobic cultures or suboptimal microbiology.

ANATOMICAL CONSIDERATIONS

Pelvic abscesses are often casually referred to as as 'tubo-ovarian' abscesses. Actually, tubo-ovarian abscesses are not common and are a distinct entity in which the process has also extended into the ovarian parenchyma. Primary ovarian abscesses are quite uncommon and are usually seen postoperatively as complications following vaginal surgery

The most common pelvic abscess is that which occurs in and around the adnexa where one wall is the broad ligament, the other the adnexa. The uterus is usually anatomically involved. This type of abscess is generally small and easily resolves with medical therapy. The larger abscesses usually occur in the posterior cul-de-sac and rarely in the anterior cul-de-sac. Posterior cul-de-sac abscesses are the most prone to peritoneal leakage. The lid is imperfect, being formed of the colon, small intestine and omentum.

CLINICAL PRESENTATION

A pelvic abscess may occur at any age. It is most prevalent during the middle of the reproductive age span (the third and fourth decade); however, it may also occur at or after menopause.

The patient with a pelvic abscess usually has been sick for some period of time and may not be able to document or give an exact description of the time or circumstances of the onset of a process. Eventually the patient will have pain, fever or lower abdominal tenderness. In some patients, there is a poor correlation between abscess size and symptomatology. On physical examination, the patient's lower abdomen is usually tender. Rebound tenderness may be present depending upon etiology and extent of disease. The pelvis is usually quite tender. Masses may or may not be identified depending upon their location and the patient's tenderness. Occasionally, the abscess may be rather high on the pelvic wall and the examiner will have difficulty feeling it from below. Usually a sense of fullness or induration can be identified. Cul-de-sac abscesses present posteriorly but sometimes are quite high and can best be felt rectally. When a posterior cul-de-sac abscess has been present for some time it may dissect into the recto-vaginal septum. On bimanual examination, the examining finger and/or speculum runs immediately into a posterior mass with the uterus and cervix displaced upward and anteriorly out of clear view.

Some, but not all of the patients, will have an elevated temperature and tachycardia. In general, the more acute the process, the more likely the patient is to have rapid pulse and fever. Patients presenting with shock have had rupture of the abscess and significant spillage into the peritoneal cavity. Interestingly enough, not all the patients will have elevated white blood cell counts (WBC) comparable to those encountered in acute phases of disease. As the process becomes subacute or indolent, the WBC returns toward normal but the erythrocyte sedimentation rate (ESR) will be elevated. The patients frequently have anorexia, nausea, sometimes vomiting, and very often diarrhea. Diarrhea is often one of the prime symptoms of the pelvic abscess. It is important to consider in the initial survey of the patient whether or not the abscess is localized to the pelvis or if the whole abdomen is contaminated. Those patients who have tenderness confined to the lower abdomen can be assumed, at least initially, to have a confined abscess. Those patients who have tenderness and/or rebound in the upper abdomen should be suspected of having a leaking or ruptured process with generalized peritoneal contamination. Persistent signs of peritoneal irritation despite hydration and antibiotic therapy dictates for an aggressive evaluation of the patient. The patient who is initially seen with shock should be resuscitated, started on antibiotics and, once stabilized, operated on.

There has been an off and on debate over the years as to whether all patients with abscesses should have immediate surgery under antibiotic coverage. Somewhere between 10 and 30% of patients who are admitted to the hospital with a diagnosis of pelvic abscess will require surgery during the initial hospitalization. Approximately one-third of these require operative intervention because the abscess has ruptured or is leaking. The rest come to surgery because they have failed to respond.

CLINICAL EVALUATION

Non-invasive imaging procedures increase our ability to be more specific in our diagnosis of pelvic abscess. In

Table 77.1 Non-invasive diagnostic technique

Detection of anatomical abnormalities	
(1)	Computerized tomography, radionuclides
(2)	Ultrasonography, human serum albumin
(3)	Magnetic resonance imaging
Detection of inflammation	
(1)	Technetium 99m
(2)	67 Gallium-citrate
(3)	WBC-Indium
(4)	IgG-Indium

addition, radionucltide scanning can be highly site specific. Computed tomography (CT) is sensitive but is expensive. Combined abdominal/transvaginal ultrasound examination is quick, relatively inexpensive, and reasonably sensitive and specific. The patient with pelvic infection and a mass or suspected abscess should have an ultrasound examination to document and measure the mass. Subsequent examinations can be useful in measuring response. Clinical evaluation includes an ESR, WBC and platelets, serum electrolytes, blood urea nitrogen, creatinine, blood culture and chest X-ray, and in the severely ill an arterial blood gas for PO_2, PCO_2, pH and central monitoring.

DIAGNOSIS

The techniques available to a clinician to identify source of infection have been divided into those that detect anatomical abnormalities (CT, ultrasonography and magnetic resonance imaging) and those that detect inflammation (radionuclide scans) (Table 77.1).

When the normal anatomy has been altered by prior surgery, damage or trauma, then a combination of techniques that demonstrate anatomical abnormality with those which detect information are added. The overall accuracy for CT and sonography in detecting abdominal abscess is in the order of 90–95%.

Ultrasonography is preferably used for diagnosing right upper quadrant and pelvic abscess. In these areas, there is no intervening bowel gas which potentially could impede sonography visualization. Patients with poorly localized abscess or in patients' postoperative open surgical wounds and drains, CT is the superior of the two methods for abscess localization.

With CT or ultrasonography, abscesses appear as complex fluid collections. However these imaging findings are non-specific and can be mimicked by hematomas, seromas, lymphoceles etc. X-ray may be used to demonstrate gas within the mass.

THERAPY

Once the diagnosis of a pelvic abscess is made, antibiotic therapy is instituted with penicillin, clindamycin or metronidazole, and an aminoglycoside. The parameters used to monitor response to therapy should include:

(1) fever;
(2) WBC;
(3) physical findings;
(4) patient's sense of well-being;
(5) the ESR; and
(6) ultasound finding

Once the titration points have been achieved, parenteral antibiotics can be discontinued. The patient should be treated a minimum of ten days, but not all of this needs to be with triple antibiotics. Most patients respond within 72 hours to aggressive systemic administration of antibiotics and fluid replacement. If therapy has been effective, the WBC count should be normal or near normal. Patients who do not improve on triple antibiotic therapy, who continue to have fever, who continue to have pain, whose mass is growing, who have persistent ileus and/or who are definitely not thriving, should be operated upon and the abscess removed and/or drained.

Those patients who do not respond to medical therapy or who deteriorate should have surgical intervention. Response equates with normalization of temperature, a normal WBC and subjective and objective improvement in the patient's condition and physical findings.

Surgical therapy has traditionally been hysterectomy and bilateral salpingo-oophorectomy. Recent experience indicates that removing only the diseased area, for instance, a unilateral salpingo-oophorectomy, is advocated. It seems clear that the standard operation of removing the uterus and both adnexa has no advantage over a more conservative surgical approach preserving potential fertility. Landers and Sweet identified a 14% subsequent pregnancy rate in patients treated with a unilateral adnexectomy for pelvic abscess. However, the incidence of ectopic pregnancies will be high in this group of patients.

With modern imaging techniques, percutaneous abscess drainage will become more commonly employed. While most of the experience thus far has been with abdominal abscesses, this method has much to offer and should be considered. In selective cases, transvaginal drainage guided by real-time ultrasonography has been shown to be a safe and effective mode of therapy (Figure 77.1).

The patient treated conservatively with antibiotics should have a pelvic examination several times a week to determine if the abscess is pointing into the cul-desac. If it does, then drainage may be achieved by a simple colpotomy. To be safe and successful in this approach, the abscess must be fluctuant, mid-line and dissecting into the rectovaginal

septum. ‘It is ready when you can’t put a speculum in the vagina because there is a mass there.’ However, it is a mistake to try to drain a pelvic abscess that has not pointed. Once a surgeon starts dissecting posteriorly in the pelvis, injury to the ureters and intestine becomes a very real possibility. If the abscess is successfully drained posteriorly and the patient thrives, it is usually enough; nothing else may need to be done.

There are some patients who will develop upper abdominal tenderness, shoulder pain, and/or shock as evidence of a leaking or ruptured abscess. These should be operated within hours of the diagnosis. In these cases, it is usually difficult to preserve either adnexa or the uterus. The wisest course is to remove the infected pelvic structures and to irrigate the abdomen copiously to remove all the pus from the entire abdomen. The latter may take liters of Ringer’s lactate. The surgeon who undertakes to operate on these patients should be quite experienced with the pelvis and with complicated

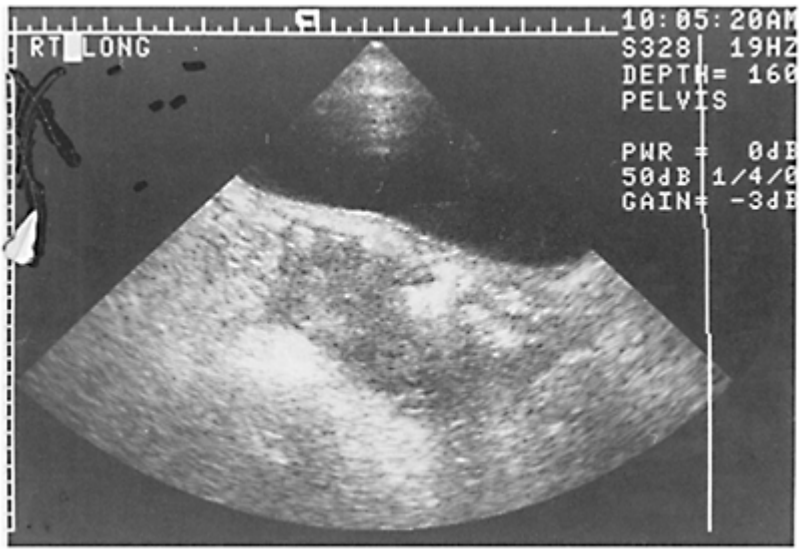

Figure 77.1 Ultrasonographic demonstration of a postoperative pelvic abscess which has the potential for fine needle aspiration (Courtesy of Susanne Granger, MD)

surgical cases because this is often a very difficult operation technically. While inspecting the abdomen in these cases, it is important to seek out intra-loop abscesses should they exist and abscesses between the diaphragm and liver. The pelvis needs to be appropriately drained. Some surgeons advocate draining the pelvis through the vagina. Having had little experience and no success with this method, I prefer to drain the abdomen in these infected cases with some type of sump drainage in the pelvis, both gutters and through the abdominal wall.

Operation intervention can be a very bloody procedure. Because of the possibility of adult respiratory distress syndrome, secondary to infection and/or shock, expert anesthesia backup is necessary. It is wise to have an ample supply of blood available. All patients should have preoperative blood gases available. Patients exhibiting any evidence of shock need a Swan-Ganz catheter. Post-operative care must be in an intensive care unit manned by an experienced team. There are a few patients whose abscesses can be drained vaginally. This is a worthwhile endeavor, quite easy to do, and in some patients this is all that is necessary from a surgical standpoint.

Operative considerations

Since the anatomy is often and perhaps always distorted, we found the best place to start the procedure is retroperitoneally over each pelvic wall. By opening the lateral pelvic peritoneum, the common and external iliac vessels can be observed and palpated along with the hypogastric artery and ureter. The abscess is almost always involved with the side wall of the pelvis. The ureter, being attached to the inferior position, is quite susceptible to injury unless it is visualized continually throughout the case. I might add that I have been called to the operating room a number of times to help surgeons deal with pelvic infection and almost invariably they had difficulty identifying anatomy and almost universally they were operating through a small incision and sometimes a transverse incision. If you are going to operate on a pelvic abscess, I recommend a midline incision which goes above the umbilicus. Adequate exposure is absolutely necessary.

The uses of gamma radionuclides however need to be understood. Iridium 11 conjugated to human IgG is suboptimal when dealing with subphrenic abscesses owing to the concentration of radionuclide in liver spleen and kidney which interferes with detection. When dealing with Gallium 67 citrate this type of nuclear type cannot be utilized in areas in close proximity to bowels.

The presence of gas within a fluid collection is the most suggestive feature of an abscess; however, approximately one-third of abdominal abscess will demonstrate this finding.

On CT, abscesses are often well defined or encapsulated areas of decrease attention (CT numbers from 0 to 20 Hounsfield units). Not infrequently these areas exhibit mass effects and displace bowel loops or impinge on adjacent structures. The sonographic features of an abscess are relatively protean. They can be anything from a complex fluid collection with fluid degree level to sonolucent masses.

Pericutaneous abscess drainage

Pericutaneous abscess drainage (PAD) of pelvic abscesses is an established radiologic procedure. The procedure has gained wide acceptance as an adjunct in the management of patients with pelvic abscesses. The procedure involves minimal trauma, is well tolerated, and produces early relief of symptoms. In many instances, it may shorten the length of the hospital stay, reduce costs, and often eliminate the need for surgical intervention. In selected patients, PAD may serve as a temporizing measure in a critically ill or endstage patient.

Patients selections

Selection of patients are predicated primarily on three criterion (Table 77.2).

Radiologically guided percutaneous drainage generally avoids the need for anesthesia in critical ill patients and can be accomplished with a relatively minimum amount of morbidity and at a fraction of the medical cost.

Table 77.2 Patient criteria for percutaneous drainage

(1)	Presence of liquefied pus that is potentially accessible by a drainage catheter
(2)	Well encapsulated abscess or an abscess within an indiscrete anatomical department
(3)	The absence of intestinal, pleural or vascular structures which would impede safe access for catheter insertion

The decision to attempt percutaneous drainage should be a joint decision reached by the therapeutic physician and the intervening radiologist. CT is the procedure of choice to stage the extent of the abscess and to determine safety of percutaneous drainage based on imaging criteria. It affords more precise visualization of the adjacent anatomy and is not handicapped by the presence of overlying bowel, surgical drainage etc.

Procedure

CT or ultrasound guided needle aspiration is performed with a 20 gauge needle. If no free flowing fluid is obtained then a larger gauge needle is inserted into the collection. Unless fluid can be aspirated from an 18 gauge needle it is unlikely that the abscess is sufficiently liquefied to be drained percutaneously.

Significant debate still exists over the suitability of multilocular abscesses for percutaneous drainage. Many multisynaptic or multilocular abscesses in fact intercommunicate with a single dominant cavity and do lend themselves to this technique. When a true multioculative abscess exists more than one catheter can be inserted. By and large the overriding contraindication to attempted percutaneous drainage is the lack of safe access because of intervening major vessels.

Management of drainage catheter

Once an abscess has been evacuated care should be utilized to ensure catheter patency. This can be achieved by injecting 10–20 ml saline through the catheter t.i.d. The parameters used to evaluate the effectiveness of percutaneous drainage include the disappearance of fever, decreased leukocytosis and disappearance of C-reactive protein and decrease in drainage volume. In most cases these parameters are anticipated to respond within 48 hours and definitely within 72 hours. Once the volume of drainage has decreased to 1020 ml per day, the catheter can be slowly advanced over several days and ultimately removed. Patients who do not respond within 72 hours need to be re-evaluated.

Complications

If one restricts observations to abdominal abscesses involving the lower pelvis, the major complications are the induction of transient septicemia with hypertension leading and surgical wound infections. In lower abdomen, the major complication is perforation or laceration of one of the mesenteric vessels.

The overall success rate for percutaneous drainage of abscesses is in the order of 85%. Recurrence rates have been as high as 8%. The key to successful percutaneous drainage of lower abdominal abscesses is a close working cooperation between intervention radiologist and the obstetrician gynecologist.

Transvaginal abscess drainage

Endovaginal ultrasonographically directed transvaginal drainage of pelvic abscesses has been utilized to treat patients who failed intravenous antibiotic therapies and whose abscesses were not amenable to percutaneous or colpotomy drainage.

The ultrasound-guided transvaginal approach offers a direct, non-surgical means for drainage of deep pelvic abscesses. It is often difficult, however, to place drainage catheters through the vaginal wall by using the Seldinger technique. Drainage procedure can be facilitated through use of a Colapinto needle as a dilator. The Colapinto needle may also served as a stiffening cannula for the passage of a fascial dilator.

Sonographically guided drainage is an effective treatment of pelvic abscess, being either completely curative or temporizing in 78% of patients. Catheter treatment was unsuccessful and surgery was necessary in 22% of patients.

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78
Wound infections

James W.Daly, MD, and Gilles R.G.Monif, MD

'If had the HONOR of being a surgeon, since I am convinced of the dangerous conditions which can be caused by the germs of microbes which are to be found everywhere, especially in hospitals, not only would I use only instruments in a perfect state of cleanliness, but also after having cleaned my hands with the greatest of care, I would flame them rapidly, a practice not much more dangerous than a smoker passing a hot charcoal from one hand to the other, and I would only use bandages, cloths and sponges which would have been exposed to air heated at 130º to 150º. I would use only water which would have been heated to 110º to 120º.'

– L.Pasteur, 1878

HISTORICAL DEVELOPMENT

Wound infection is a problem as old as mankind. It was only in the latter half of the nineteenth century that wound infection was recognized as a disease process in itself. Until that time, infection and inflammation seemed inevitably to go hand in hand and were generally considered a single process in wound healing. Various salves, ointments, noxious concoctions, incantations, and prayers all have had their place in the art of promoting wound healing or preventing certain types of infections or inflammations. The physician or surgeon, until quite recently, has anxiously awaited the appearance of laudable pus'.

Galen, the famous Greek physician, was appointed surgeon to the gladiators of the city of Pergamon early in his career. He found that, when treating the wounds of gladiators (especially the incised wounds), if he washed them with wine, removed the blood clots and foreign material, and sutured them, many healed without suppuration. For some unknown reason this observation was neither disseminated nor practiced, and he later advised the introduction of ointments and drugs that favored the formation of laudable pus and healing by secondary intention. Because Galen became the infallible authority in medicine and surgery, this doctrine of healing by suppuration became the accepted one until the time of Lister. Perhaps Galen observed that some wounds rapidly proved fatal before pus appeared, for example, wounds infected with virulent streptococci or gas bacilli, but that wounds left open, with pus formation, healed, although the healing process was dilatory. Whatever the reason, Galen's conclusion was that suppuration is an essential part of wound healing. Some of his observations are accurate. We have found

that leaving the contaminated wound open is the best method of management but that suppuration is not necessary for healing.

Several military surgeons in the thirteenth and sixteenth centuries advocated primary wound healing and wound closure. But the doctrine of laudable pus and healing by secondary intention remained the basic doctrine of wound care. Such diverse objects as unicorn's horn, mummy's skin, boiling oil, and a hot cautery were recommended not only to decontaminate wounds but to promote healing. One of the most successful methods of wound treatment in the fifteenth and sixteenth centuries was the use of weapon salve. This melange consisted of various noxious and magical ingredients and was carefully applied to the weapon which caused the wound. The weapon dressing was changed every third day until the patient's wound was healed. Meanwhile, the wound itself was covered with a linen dressing and forgotten. During the same period, bandaging of wounds became important, and one of the bandages devised by a German surgeon, Scultetus, is still in use today.

Table 78.1 Classification of wounds based on the degree of contamination

Degree of contamination	***Type of wound***
Clean	Elective surgery, non-contaminated No drain
Clean contaminated	Operations on the gastrointestinal tract Cholecystectomy Hysterectomy
Contaminated	Operations in an area with acute inflammation but no pus Spillage from the gastrointestinal tract Major breaks in technique
Dirty	Operations in an area with pus Peritonitis Perforated viscus

(National Academy of Sciences, National Research Council Cooperative Study Ad Hoc Committee on Trauma, Division of Medical Sciences. *Ann Surg* 1964; 160(Suppl 2):11)

It was not until the nineteenth century, following the development of the microscope, when Koch, Pasteur, and Lister established the bacterial etiology of wound purulence, that the principles of healing, inflammation, and bacterial infection were separated and incorporated into medical practice. According to current concepts, we expect the cleanly incised surgical wound to heal by primary intention, and we go to extraordinary lengths to prevent infection. However, since the acquisition of an armamentarium of antibiotics, we sometimes forget that infection is a surgical threat. We have delegated much of the responsibility for the prevention of infection to others, such as the ward nurse and the operating room personnel; as physicians we forget that this facet of management of the patient is primarily our responsibility.

DEFINITION OF WOUND INFECTION

A wound infection can be defined, after Ljungquist, as a collection of pus which empties itself spontaneously or after incision; it is usually associated with intense redness, infiltration, and elevated temperature of the wound. Traditionally, wounds have been classified on the degree of contamination (Table 78.1).

EPIDEMIOLOGY

The source of bacteria recovered postoperatively from a wound infection is most commonly the patient herself, either from the skin surface, from adjacent mucosal surfaces, or as a contaminant from the gastrointestinal tract or an abscess cavity.

A second, less likely source of contamination is the skin of the surgeon and assistants, particularly as it comes in contact with the wound through frequently torn gloves. It has been estimated that in 50% of operative cases the surgeon's or assistant's gloves are torn. Bacteria can traverse a blood- or sweat-soaked surgical gown, another potential source of wound contamination. Many modern gowns are therefore waterproof in the arms and front. For several years we have worn plastic aprons under our gowns, which may have contributed to a lessened wound infection rate. On occasion the nasopharynx of the people present in the operating room can be a source of wound sepsis, but the modern paper mask is 90% efficient. Cloth masks are less so, and tend to be worn longer. The air and environment in the modern operative suite is rarely implicated in surgical infection. The traditional preoperative shave may be a source of wound infection, particularly if done the day before surgery. The inevitable small nicks and scratches become infected and may provide the nidus of future infection. Shaving the area immediately before surgery or simply not attempting to remove the hair are all associated with a lessened wound infection rate.

INCIDENCE

The incidence of wound infection in clean operative cases varies from 2% to 5% and generally remains constant from hospital to hospital. Most abdominal gynecologic procedures are in the clean-contaminated category and occasionally are grossly contaminated. Any time the vagina is opened from above, the area must be considered as contaminated. Historically, the rate of postoperative wound sepsis in abdominal hysterectomy usually ranges between 3% and 6% while Cesarean section is somewhat higher—ranging between 4% and 8%. With the aggressive and proper use of preoperative antibiotic prophylaxis, these rates have been significantly reduced.

PATHOGENESIS

Healthy tissues have a remarkable resistance to bacterial contamination. For infection to occur, it requires one of four conditions to be met:

(1) unique ability on the part of the bacterial pathogen to circumvent or negate local host resistance, e.g. group A beta-hemolytic streptococci;
(2) the amount of contamination is over-whelming both in terms of the numbers of organisms and of lowering the local redox potential, e.g. feces;
(3) two or more bacteria function in a synergistic manner, e.g. Meleny Type II ulcer-progressive synergistic bacterial gangrene; or
(4) placement of a foreign body, e.g. suture or drains *(Staphylococcus aureus).*

Until granulation tissue has formed, the surgical wound is a spectrum which varies from healthy to devitalized tissues. Dead and devitalized tissue has little, if any, ability to impede significant bacterial replication. It is a major key to the anaerobic component of wound infection. The low oxidation-reduction potential of dead or devitalized tissue allows for the preferential recruitment of organisms which have the ability to grow at a low redox potential and in the diminished presence of molecular oxygen.

The presence of dead or devitalized tissue within the wound environment is the consequence of one or more of the following mechanisms:

(1) crushing injury or trauma caused by a clamp or tie;
(2) iatrogenic impairment of the regional blood supply by ligation or compromise of relatively large vessels or suturing under tension; or
(3) creation of anatomical dead spaces, e.g. hematomas and seromas via incomplete hemostasis.

MICROBIOLOGY

The microbiological data derived from studies of wound infections prior to the late 1970s are flawed by the use of inappropriate culture techniques which impeded isolation of class II and class III anaerobic bacteria.

A postoperative wound infection is caused by bacteria that gain entrance to the incision—admittedly a simplistic statement, but it is only since the turn of the century that this has been universally recognized. The source of the bacteria is most commonly the patient: from the skin surface, the adjacent mucous membrane, the gastrointestinal tract, an abscess cavity, the vagina or the endocervix. A second but much less likely source of wound contamination is the skin or nasopharyngeal tract of the surgeon and/or assistants.

Wound infection may also be due to a concomitant infection in a distant site such as the kidney or respiratory tract and an associated bacteremia contaminating the incised wound.

Most postoperative wound infections are polymicrobial in nature rather than due to a single bacterium. Admittedly, the bacteriology of wound infections is poorly delineated if inappropriate sampling techniques are applied. The literature would indicate that the most common organisms in wound infection are *Staphylococcus aureus, Staphylococcus epidermidis,*

Table 78.2 Principal bacteria which may produce monomicrobial abdominal wound infections

Clostridium perfringens
Clostridium sordelii
Haemophilus influenzae
Streptococcus, groups A, B, C, F, and G
Staphylococcus aureus
Staphylococcus epidermidis

Escherichia coli, Bacter-oidaceae, Proteus mirabilis and *Pseudomonas*.

The simple swab culture technique is biased toward predominantly aerobic bacteria. On the other hand, if the tissue biopsy technique is used or if anaerobic methods are used to culture the wound, the percentage of anaerobic bacteria in the given wound rises. The best method for culturing a wound infection is to debride a small amount of necrotic tissue and use it as the culture specimen. If a significant amount of pus is present, an aspirated sample submitted in a syringe without air inclusion is the preferred method of culturing.

S. aureus and the beta-hemolytic streptococci can function as mono-etiologic agents. *S. aureus* is one of the few bacteria in wound infections that may be monomicrobial or polymicrobial. Monomicrobial disease involves aerobic bacteria of enhanced virulence or the staphylococci. Polymicrobial wound infections are a function of synergistic bacterial coupling or the anaerobic progression.

Monomicrobial wound infections

The prime monomicrobial bacteria causatively associated with abdominal wound infections are listed in Table 78.2.

With iatrogenic disruption of the cutaneous barrier, exogenous and endogenous bacteria with enhanced virulence gain potential access to subcutaneous tissue planes and their endolymphatics. These anatomical structures provide the avenues for lateral spread. A prime example is necrotizing fasciitis and erysipelas-like disease emanating from wound margins due to the group A or B streptococci.

Polymicrobial wound infections

The oxidation-reduction potential of healthy tissues constitutes a primary barrier to most bacteria lacking augmented virulence factors.

For polymicrobial wound infection to evolve, some critical change in the microbiological environment must occur. Given the appropriate microbiological environment at the operative site, synergistic interfacing of bacteria may result in the induction of disease. The majority of abdominal wound infections occurring after Cesarean section are observed in women who had prolonged rupture of the fetal

membranes and/or prolonged stimulated labor, owing to a quantitative augmentation of the associated amnonitis.

When bacterial coupling involves an aerobic bacterium of augmented virulence with an anaerobic bacterium, e.g. *S. aureus* and a microaerophilic streptococcus, *Streptococcus millerii* and a *Bacteroidaceae* (progressive synergistic bacterial gangrene) or an *Enterobacteriaceae* with a *Bacteroidaceae* (Daly's syndrome), a significant gangrenous wound infection may ensue.

Numerically, the majority of abdominal wound infections are the consequence of some variant of the anaerobic progression. Necrotic tissue and/or microhematoma formation in conjunction with bacterial contamination are the prime catalytic factors initiating disease.

Toxin-related wound infections

Both *Clostridium perfringens* and *Clostridium sordellii* have the capability of producing a unique type of wound infection. The syndromes produced by both *C. perfringens* and *C. sordellii* are mediated primarily through exotoxins and require only the establishment of infection. Neither bacterium appears to require the initiation of the anaerobic progression for disease to evolve. Given the proper microbiological environment, exotoxinmediated disease with the induction of systemic symptology as well as lateral and vertical spread through tissue planes occurs. The microbiological environment is

Table 78.3 Factors contributing to wound infections

Obesity	Adipose tissue is relatively avascular and consequently less likely to overcome even a small bacterial inoculum
Malnutrition	Protein deprivation significantly retards wound healing
Hypoxia	Both chronic (anemia) and acute (shock) as well as excessive pressure on the side of the wound due to retractors
Impairment to host defense mechanism	Diabetes mellitus (insulin dependent) Prior radiation to operative site Chemotherapy Corticosteroids
Shaving operative site	Shaving of indicated area should be done just prior to the operation and NOT the night before surgery
Incomplete hemostasis	Enhances anaerobic replication and provides a potential site for abscess formation
Length of operation	In contaminated cases, the incidence of infection begins to rise steeply if the operation lasts more than two hours
Foreign bodies	Highest incidence of wound infection is associated with cotton and silk sutures (plain catgut promotes the most inflammation)
Drains	Particularly if the drains come out through the incision

a critical factor in initiating disease. Both of these species of clostridium are relatively common in nature in contrast to the rarity of disease due to these bacteria.

CONTRIBUTING FACTORS

The patient

A large number of factors are though to increase the probability of ensuing abdominal wound infections. These factors are summarized in Table 78.3.

In addition, clinical experience indicates that cancer, even remote from the surgical area, enhances the risk of infection. This may be related to a depressed immune mechanism, malnutrition, and hypovolemia as well as the type and length of the operation. Prior radiation to the abdominal wall can also facilitate wound infection (Daly's syndrome). Radiation injury to the stroma is primarily one of vascular obliteration with time. Initially, the endothelial cells are damaged; they become edematous and eventually are destroyed and replaced with fibrous tissue. During radiation therapy, and for the first 4–6 weeks afterwards, there is actually a net increase of tissue perfusion because of the inflammatory changes associated with the initial radiation insult. However, over time the inflammatory response subsides and an eventual loss of vascular supply to the area results. Therefore, the wound that has been irradiated in the distant past has a relative lack of tissue perfusion, which is an important determinant of wound infection.

The surgeon

Perhaps this section should be entitled Trauma', but the surgeon creates it and must be responsible for the result. Each wound infection is iatrogenic—the ultimate goal is perfect healing with a 0% wound infection rate. Therefore, part of the surgeon's attention should be directed to this goal before, during, and after the operation. He (more often now, she) must be cognizant of local wound factors.

A cleanly incised wound offers less damaged tissue than a terraced incision (the neophyte will make multiple strokes of varying depth and pull the knife toward himself, producing a terraced slope resembling an Austrian vineyard—this produces bleeding, and the surgeon, losing his way, produces another valley, the bottom of which is not the abdominal fascia, but a cavern excavated beneath the skin on his side of the table). Large bites of the hemostat or vigorous cauterizing of bleeders produces an abundance of necrotic tissue, a happy commune for opportunistic bacteria. There continues to be a low-key debate regarding ligature or cautery of wound bleeders. This author favors ligature but either method used with precision and delicacy is suitable. The point is to control bleeding, leaving a minimum of necrotic and foreign material in the wound. Halstead demonstrated that staphylococci could be injected into the leg muscle of a dog without causing infection, yet when the same bacteria were injected into a previously crushed muscle, an abscess invariably resulted. He was an early proponent of fine technique and gentle handling of tissue. Foreign bodies in wounds have been known for centuries to be promoters of suppuration. In this century the military surgeon has taught us to debride

dirty wounds, remove the foreign material, and leave the wound open for secondary closure. In civilian practice the most common foreign body in the incision is suture material. The degree of inflammatory response (an attempt at rejection) to different types of sutures is greatest for chromic and plain catgut, least for steel, and intermediate for cotton, silk, and synthetic material. The finer the suture, the less the total tissue reaction.

Decreased local wound perfusion is associated with an increased incidence of wound sepsis. This may be associated with a decreased circulatory blood volume, shock, anemia, or local factors; for instance, adrenalin infused locally causes vascular spasm, a dramatic drop in local perfusion and, on an experimental basis at least, an enhanced infection rate. The general and non-specific inflammatory response of a wound is dependent on local circulation. Excessive pressure on the sides of the wound by metal retractors can cause not only decreased local perfusion but actual crushing and damage to the tissue. Anesthesia plays a part here in that a properly placed retractor can suddenly produce an excessive pressure on the side of the wound if the patient's level of anesthesia changes and the abdominal musculature becomes tight. Therefore, good anesthesia with adequate relaxation throughout the procedure can prevent wound infections.

Drains and bowel stomas entering the primary operative site act as foreign bodies in the wound and as carriers of bacteria from the inner and outer sides of the wound. Therefore, drains and stomas should not be brought through the primary operative site if at all possible, but through a separate opening. Drains in the subcutaneous space really drain very little, but do act as a foreign body and as a portal of entry for bacteria from the skin and environment into the subcutaneous tissue.

It is particularly important to preserve fine vesseled areolar connective tissue about the fascia since it nourishes and vascularizes the fascia. The fascia itself has no blood vessels.

Vigorous stripping or cleaning of the fascia retards healing and promotes infection. Likewise, grasping the fascial edges with a crushing clamp, such as a Kocher, will crush the tissue and may act as a site for bacterial growth.

COURSE AND DIAGNOSIS

The majority of patients with a postoperative wound infection will have an elevated temperature which begins on the day of surgery or the day after. The temperature curve is such that the bottom never reaches normal. Early in the process, examination will show little, and other causes are frequently thought to be responsible for the fever, such as pulmonary complications or a urinary tract infection. As the infection advances, the temperature, on the third, fourth, or fifth day, will reach higher levels. By this time, all or part of the wound becomes tender and inflamed, and eventually pus will escape. This may occur prior to or during removal of the skin sutures. When the wound is inflamed and tender it is useful to put warm, moist packs on the incision; this often speeds up the process of bringing pus to the surface.

Some abscesses, however, are subfascial and due to anaerobic bacteria, which grow slowly. The patient may have an intermittent fever that lasts for days or weeks without any local sign until pus finally escapes through the fascia into the subcutaneous tissue. This is followed by the rapid development of a tender, inflamed area in the abdominal wall. We refer to this as a collar-button abscess (Figure 78.1).

Wound infection due to the coagulase-positive betahemolytic streptococcus manifests itself quite early by severe temperature elevation, toxicity, and extreme inflammation in the area of the incision. This picture will give a clinical indication of the organism even before the cultures have been returned. In all cases of

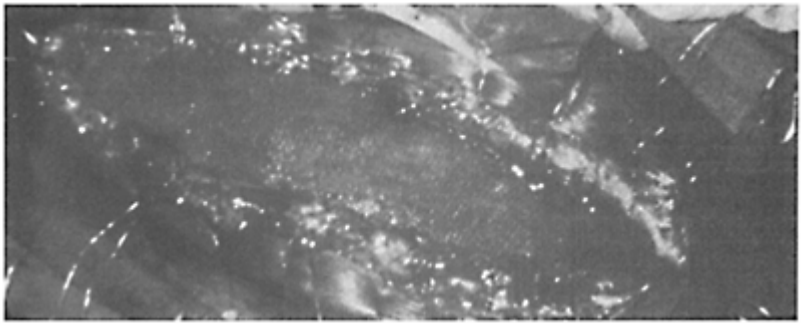

Figure 78.1 Subfascial collar-button abscess

wound infection, aerobic and anaerobic cultures should be obtained as soon as pus is present. The necrotizing wound infections usually begin in the same way as the more common wound infections but later show an undermining and purple discoloration of the surrounding skin. There is also a loss of considerable amounts of tissue from the abdominal wall.

TREATMENT

Antibiotics are generally ineffective in treating an established wound infection. When the diagnosis is suspected owing to swelling, redness, and tenderness of the area, heat frequently will accelerate the process and bring the pus to the surface. Once the purulent material has begun to escape from the wound it should be cultured aerobically and anaerobically, and if there is anything more than a very superficial abscess under the skin margins, the entire wound, or at least that part of the wound involved, should be opened widely. We prefer to do this in the operating room under anesthesia. It is much more comfortable for the patient, and the wound can be thoroughly investigated and adequately debrided. Occasionally an infection is associated with a dehiscence, and it is embarrassing and dangerous to open the patient's wound on the hospital ward and to have the bowel pour out from the abdominal cavity along with the pus.

With the wound opened, the area is generally irrigated with normal saline solution and the necrotic material is then debrided. Fascial defects are sought out and subfascial abscesses opened. The peritoneum is usually found to be quite thickened in these cases. Once the patient's wound is debrided and cleaned, it is packed with moistened sponges. If the fascia has been opened, it is wise to keep the patient at bed rest until the base of the wound has become thoroughly granulated. During the active phase of treatment, when

pus is present, we like to use hydrogen peroxide as well as saline to irrigate the wound. Some physicians pack the wound with iodboform gauze but the iodine crystals may be toxic to tissues and seriously interfere with the establishment of the local circulation and granulation tissue. This may also be true of hydrogen peroxide, so that once pus is absent from the wound, only saline should be used for irrigations.

The wound ablutions and packings are repeated four to five times each day. It is necessary to have the gauze sponges packed into all the crevices of the wound so that they adhere to the surface; when they are removed they will remove surface debris and mechanically stimulate the granulation tissue.

If, on the other hand, the surgeon chooses to let the wound heal secondarily, this can be cared for at home. The rate of wound contracture and healing depends to a large extent upon the patient's nutrition, general health, and age. However, the wounds generally close rapidly. The resulting scar is somewhat broader than that produced by a primarily healed incision but is usually

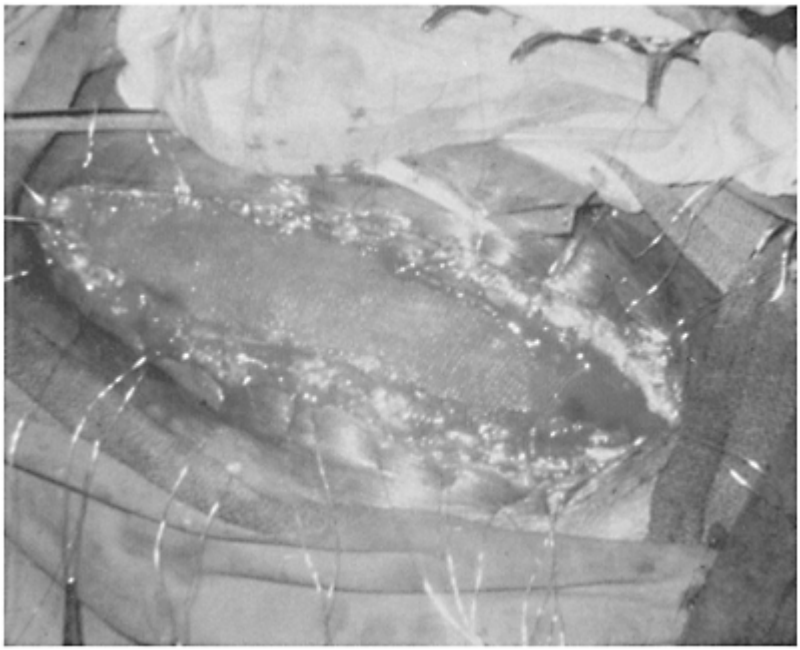

Figure 78.2 Closure of an abdominal wound defect with Marlex mesh which is sewn to the fascial edges with wire sutures

much more satisfactory than either the patient or the physician anticipates.

Evisceration

When evisceration occurs through an infected wound, surgical intervention must be immediate. With the patient anesthetized the abdominal cavity is copiously irrigated with saline and the wound debrided and closed in one layer with wire retention sutures. We have found that heavy silver wires which are twisted rather than tied are useful. This type of suture creates a minimum of local tissue reaction and can be easily loosened as the wound swells. On occasion definite layers in the abdominal wall can be ascertained and then it is possible to close the fascia and the peritoneum together, using the Smead-Jones technique with the skin left open. As we have indicated above, systemic antibiotics should be administered, based on the cultures, since peritoneal contamination is inevitable. If, however, culture information is not available, it is best to start the patient on triple antibiotic therapy.

When tissue destruction is extensive, the bowel may be exposed but not actually eviscerated. The necrotic tissue should be debrided under anesthesia and either the wound is closed primarily or, if this is not possible, Marlex mesh is sewn to the fascial edges with nylon or wire suture, the Marlex is covered with moistened sponges and abdominal pads, and is held in place with Montgomery straps. Once the wound is clean and the infection has subsided, the Marlex can be removed and the wound closed primarily (Figure 78.2).

NECROTIZING WOUND INFECTIONS

Necrotizing infections include the monobacterial ‘clostridial’ and the multibacterial synergistic infections, which the literature addresses as necrotizing fasciitis, synergistic bacterial gangrene and Daly’s syndrome.

The synergistic infections usually appear in a predisposed host, such as the diabetic, the malnourished, or the immunosuppressed patient, and in the area of radiation injury. The necrotizing infections of interest to the gynecologist include those which occur after episiotomy and operations through the abdominal wall. The destructive process can occur spontaneously in both of these areas.

Necrotizing fasciitis (acute hemolytic streptococcal gangrene wound erysipelas)

Necrotizing fasciitis, now a relatively rare disease, was recognized during the American Civil War as ‘hospital gangrene’ and was associated with a high mortality rate (46%). By 1918 Pfanner identified the betahemolytic streptococcus as the causal agent and called the disease process necrotizing erysipelas. In 1924 Meleney reported 20 cases and called the process acute hemolytic streptococcal gangrene. He confirmed the beta-hemolytic streptococcus as the cause. The present term, necrotizing fasciitis, is from a 1952 report by Wilson, who found other organisms in his cases.

Nevertheless, the basic pathologic process is a subcutaneous necrosis of the fat and fascia with a secondary occlusion and thrombosis of the dermal vessels, leading to

eventual gangrene of the skin. In the classic case (due to beta-hemolytic streptococci), the local toxin is a macromolecular complex of mucopolypeptides and polysaccharides. The bacterium also produces hyaluronidase, which may account for the rapidly spreading cellulitis. As the pathologic process continues, areas of necrosis offer a favorable medium for the growth of secondary invaders, both aerobes and anaerobes, which may overgrow the beta-hemolytic streptococci *in vitro*. The beta-hemolytic streptococcus was the predominant organism in the preantibiotic era. More recently, other causative organisms, usually in mixed cultures, have been incriminated. At times it is difficult to differentiate necrotizing fasciitis from synergistic bacterial gangrene on bacterial and clinical grounds. With the exception of the pure betahemolytic streptococcal gangrene, they are probably the same entity. The majority of cases (80%) occur after minor trauma or insignificant injuries, usually involving the extremities. While diabetes, atherosclerosis, and a suppressed immune status (from cancer, chemotherapy etc.) seem to be common factors, disease occurs in previously healthy individuals. Necrotizing fasciitis has been described after spontaneous vaginal delivery (where episiotomy provide the portal of infection), post Cesarean delivery, post laparoscopic surgery and a variety of minor surgical procedures involving the vulva. The incidence of disease fluctuates with the prevalence of the group A streptococcus in the community. Attack rates of 1.8 per 1000 women undergoing Cesarean section have been identified. Often infection initially presents as what appears to be mild, innocuous cellulitis. Delays in recognition of what is a rapidly progressing infection and in instituting aggressive surgical management results in increased morbidity and mortality. A delay greater than 48 hours between initial recognition and treatment may result in up to 60–70% mortality.

The acute fulminant postoperative case does occur but, fortunately, rarely. Within 24–48 hours after the operation the patient will have a high temperature and be acutely ill to the point of disorientation. The wound and surrounding tissue is fiery red, swollen, and very tender. Blebs or blisters eventually appear, surrounded by blue or black areas of necrosis. Streptococci can often be cultured from the blebs. Over half of the patients will have positive blood cultures. Early in the disease process there is extensive subcutaneous and fascial necrosis with undermining of the skin (thus the blotches of necrotic skin). In the classic case, gray or serosanguineous fluid exudes from the wound. The cases with mixed infections frequently have pus present. The muscle tissue is usually spared. During this time of fever, toxemia, and massive destruction, fluid may shift into the involved area at the expense of the vascular compartment, with associated electrolyte imbalance. Serious serum calcium deficits have been reported due to sequestration into the area of fat necrosis.

In most instances C-reactive protein values will be markedly elevated with values often exceeding 200 mg/l. Biochemical markers of disseminated intravascular coagulopathy may be present. Cases of a toxic shock-like syndrome characterized by a generalized maculopapular rash, hypotension, respiratory distress and renal hepatic abnormalities have been described in patients with necrotizing fasciitis involving the female genital tract. The diagnosis of necrotizing fasciitis is usually made by a combination of clinical features and recovery of an M-serotype isolate of the group A beta-hemolytic streptococci. The demonstration of asymmetric fascial thickening and soft-tissue gas are supportive of the diagnosis.

Using MRI technology, hyperintense T2-weighted signals within deep fascial planes is supportive of the diagnosis; however abnormally high signal intensity is not specific for necrotizing soft tissue infection. A variety of non-necrotizing conditions can produce similar findings.

The primary therapy is immediate operative debridement in the operating room under anesthesia. The incision is opened and all necrotic skin and subcutaneous tissue is removed (Figure 78.3).

Aerobic and anaerobic cultures of wound (pus and tissue) and blood are important. High-dose penicillin therapy (20 million units/day IV) should be started when there is marked cellulitis, severe toxicity, or a positive blood culture. In the cases with mixed infection (foul pus), antibiotics are not effective unless the patient is septic or has a positive blood culture.

The immediate need is surgical debridement; these are emergency cases. Delay to await culture reports or to try antibiotic therapy or local wound care is futile and leads to massive tissue loss with bowel exposure, sepsis, peritonitis, and death.

Once the wound is debrided, local wound care is given as indicated for the more benign infections. Since there is usually considerable fascial loss, postoperative hernias are common. If a full-thickness debridement is necessary, a Marlex graft can be placed and removed later with secondary wound closure.

Progressive synergistic bacterial gangrene

This gangrenous wound infection was reported by Cullen in 1924 and reaffirmed by Brewer and Meleney in 1926. The majority of cases have followed operations involving abdominal abscesses or bowel procedures and closure by retention sutures (Figure 78.4).

The earlier cases were all associated with a microaerophilic or anaerobic streptococcus in the outer rim of induration and a hemolytic staphylococcus in the central area of slough. Animal experiments indicate that either organism alone does not produce the clinical picture, but when acting together in the same wound they apparently work synergistically even though, or perhaps because, they have very different oxygen requirements. More recently, similar wound problems have been described with anaerobic streptococci and various Gram-negative organisms *(E. coli, Proteus, Pseudomonas, Klebsiella)* as the aerobe, and some with *Bacteroides* as the anaerobe coupled with Gram-negative aerobes. It would appear that the presence of aerobic and anaerobic organisms in the infected area is the requirement for synergism rather than the species of bacteria. As opposed to necrotizing fasciitis, the course in progressive synergistic bacterial gangrene is indolent (‘chronic gangrene’) and usually not associated with marked systemic toxicity. Early, the wound is quite painful, with an outer erythematous indurated rim surrounding an ever-enlarging area of necrosis. There is undermining and gangrene of the skin and eventual destruction of the underlying fascia and muscle. The process becomes clinically apparent on the fourth or fifth postoperative day, but only after 10–12 days is it obvious that a gangrenous synergistic process is present. The classic case enlarges at the rate of 1–2 cm/week. However, some of the infections populated by *Bacteroides* and Gram-negative aerobes can be very rapid and aggressive, with invasive tissue destruction in width and depth associated with more systemic toxicity. These infections are difficult to separate from necrotizing fasciitis

except that synergistic bacterial gangrene of the aggressive variety involves the full thickness of the abdominal wall, with destruction of all tissues at an even rate. While the majority of these infections follow surgery, they have been noted to occur spontaneously in Bartholin's gland and the abdominal wall.

Treatment is based on wide surgical removal of the infected area, including the erythematous outer margin. The excision must be deep enough as well as wide enough to remove the entire infected area. This may leave a large defect in the abdominal wall, which can be closed with Marlex and the wound closed primarily several weeks later. Antibiotics are probably not useful or necessary unless the patient is septic. Cases have been treated with hyperbaric oxygen. While not effective in cases of necrotizing fasciitis, hypertonic oxygenation

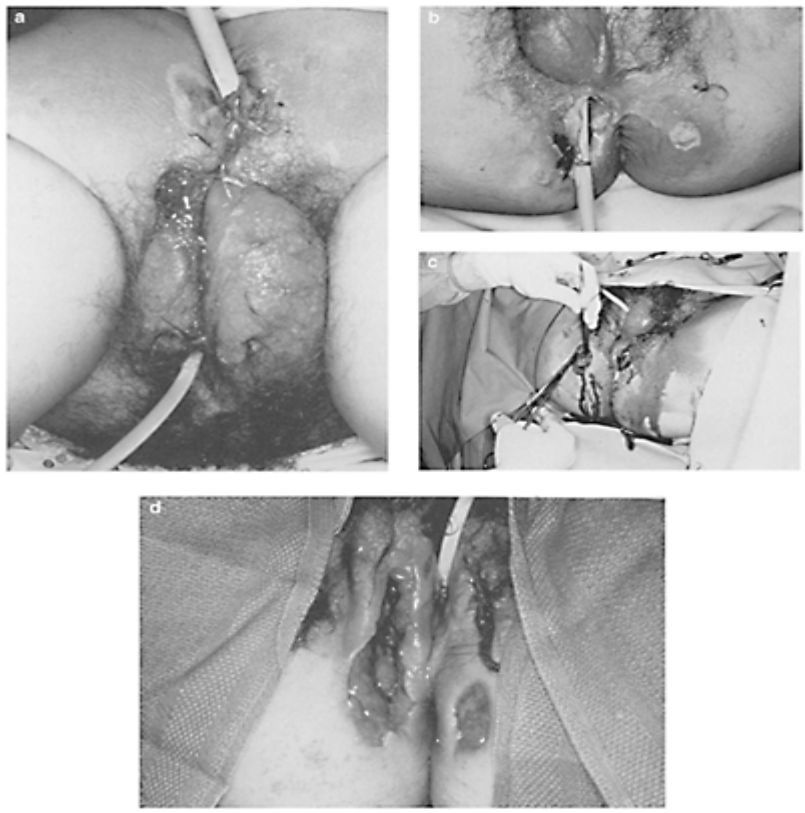

Figure 78.3 Necrotizing fasciitis. (a) Patient with necrotizing fasciitis. (b) Degree of resolution achieved with antibiotic therapy. (c) Operative debridement. (d) Lesions post surgical debridement

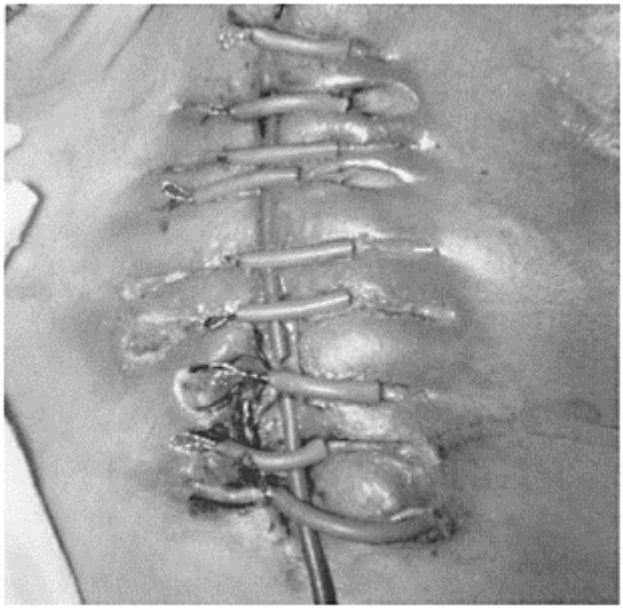

Figure 78.4 Progressive synergistic bacterial gangrene. Abdominal wound 14 days after secondary closure with stainless steel wire. Note the marked edema at the wound's margins and gangrenous areas around the sutures (deLongh DS *et al. J Am Med Assoc* 1967; 200:557)

therapy is a potentially valuable adjunct in patients with progressive synergistic bacterial gangrene and *Clostridium perfringens* induced necrotic infections.

Monif and Daly have described the counterpart of Fournier's disease (spontaneous occurrence of progressive synergistic bacterial gangrene) in women. This disease entity occurs primarily in diabetic patients in the areas of the Bartholin's gland or abdominal wall. These patients are treated by wide surgical excision of the area of involvement. Of interest is that in the cases involving the abdominal wall, the fascia is usually not involved (Figure 78.5).

Postirradiation necrotizing wound infection

We have noted a third type of destructive wound process in patients who have received radiation therapy for cancer. We have called it postirradiation necrotizing wound infection. These infections occurred in the irradiated field at least six weeks after the radiation therapy. The wound dissolution was apparent by the third or fourth day

following abdominal surgery although the patients had no fever, pain, or systemic toxicity. The loss of tissue from the full thickness of the abdominal wall was from 1 to 3 cm/24 hours. That portion of the incision that extended beyond the irradiated field was not involved. The wounds were not purulent. In all cases the bowel was exposed. In several earlier patients the process proceeded to rapid destruction of all the abdominal wall within the radiation port, then stopped. These patients developed bowel fistulas and peritonitis, and died.

The bacteriology of these wounds (derived from central and marginal tissue samples) revealed *Bacteroides fragilis* and *E. coli* in each case, together with a variety of other aerobes and anaerobes such as *Pseudo-monas,* anaerobic streptococci, *Klebsiella,* and *Proteus mirabilis.*

This wound infection, like the other gangrenous infections, must be excised widely to bleeding, well-vascularized margins. Since a full-thickness excision is done, closure is usually not possible, so a Marlex mesh is sewn to the fascial edges of the wound. This allows the patient to ambulate and serves as a prosthetic fascia. The Marlex is covered with sponges and pads. Eventually the epithelium will migrate from the edges, or the area, when granulated, can be grafted. In one case, relaxing incisions were made outside the irradiated field and the wound was successfully closed secondarily. This is not usually possible because of the rigidity of the irradiated area.

As in all other gangrenous wound infections, rapid recognition and immediate (at night if necessary) and bold excision results in less loss of abdominal wall, a better cosmetic result, and less mortality. The ability to replace the excised abdominal wall with Marlex mesh allows one to be bold (Figure 78.6).

GENERAL CONSIDERATIONS

In preventing wound infection, a number of things should be taken into consideration and should become part of the surgeon’s plan and technique.

Do not use a lot of force in scrubbing the operative site in the operating room. This local irritation is associated

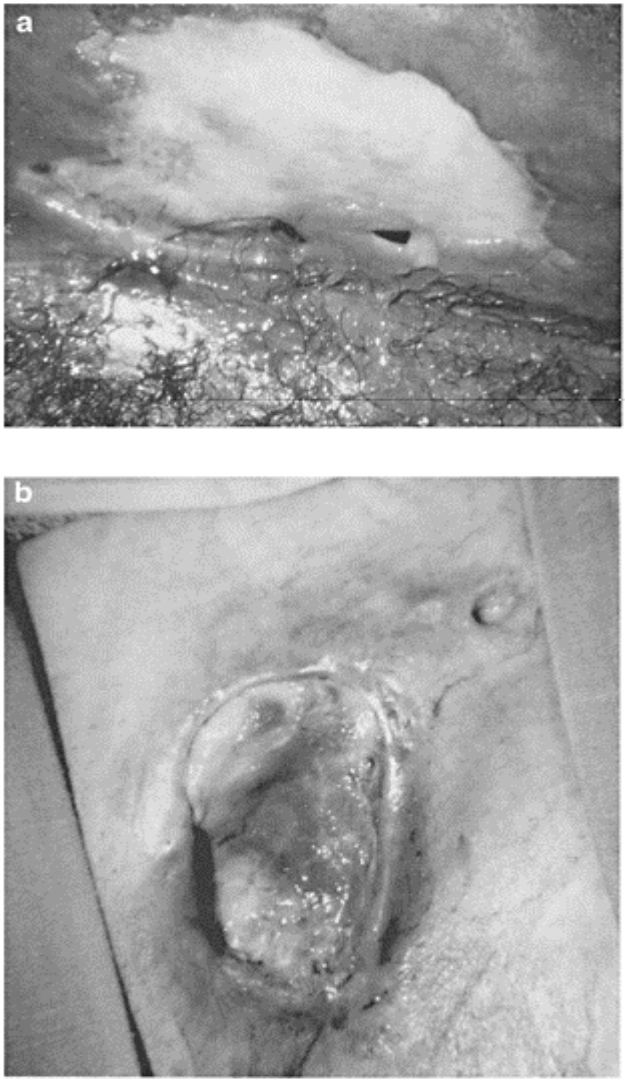

Figure 78.5 Spontaneous synergistic wound infections. (a) Occurrence in the abdominal wall. (b) Occurrence in the inguinal groin area. Note in both cases the presence of a fistulous tract. (Daley JW, Lukowski MJ, Monif GRG. *Am J Obstet Gynecol* 1978; 131:624)

with a dilatation of the vessels under the skin. This in turn causes more bleeding. **Do not clean off** the fascial layers since the blood supply to this area will be decreased. In the excessively obese and certainly in contaminated cases, it is wise to close the fascia and peritoneum and leave the skin open for closure in four or five days. **No free space** should be left in the wound and hematomas are to be prevented. The best type of closure for the abdominal incision, particularly in disadvantaged patients, is the far-and-near or Smead-Jones type closure, where the peritoneum and fascia are closed in one layer, or mass closure with running technique.

Prophylactic antibiotics

Local

Irrigating the incision with saline may wash out foreign material such as blood clots and other foreign matter, but the bacteria are unaffected and saline irrigations do not influence wound infection rates. Experimental and clinical data indicate that povidone-iodine, ampicillin, neomycin, tetracycline and kanamycin sulfate are all effective in lowering infection rates, particularly in those patients who are at high risk. One must be cautious, however, in using these agents, particularly neomycin, since they are absorbed from the tissue. Specifically, in the case of neomycin, toxicity and nephrotoxicity have been reported secondary to local wound irrigation.

Systemic agents

In recent years a number of studies with regard to prophylactic antibiotics have been and are being published, but the data with respect to wound infection rate are mixed. To be effective, the prophylactic antimicrobial should be administered long before bacterial lodgement has occurred. Animal data indicate that the effective period of preventive antimicrobial action in the wound is quite short, beginning the moment the bacteria gains access to the wound and ending within about three hours. The presence in the wound of a suture or other foreign material considerably limits the activity of the antibiotics. Penicillin, ampicillin and the cephalosporins diffuse slowly into the wound and are present in the wound fluid within one hour. Clindamycin, on the other hand, takes two to four hours to show an appreciable level in the wound fluid, while carbenicillin, nafcillin, amoxicillin, gentamicin and erythromycin still have very little concentration as much as five hours after administration.

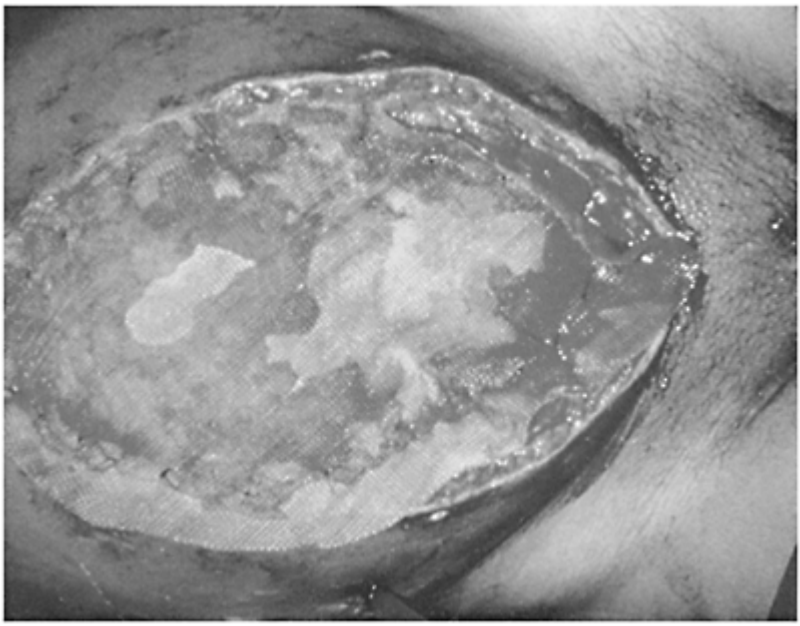

Figure 78.6 Replacing the excised abdominal wall with Marlex mesh. A large abdominal wall defect created by full thickness resection of necrotic tissue back to bleeding margins in a case of post-irradiation necrotizing wound infection

Operative field

It is our practice to have the patient shower, or at least have the operative area washed, with an iodophor soap on the night before surgery. We have given up the surgical shave on the night before. For a time we were using depilatories and found this to be a suitable method of hair removal, but some patients reacted to the depilatory with local dermatitis. Therefore, at the present time we do not have patients shaved at all, and have not seen any increase in wound infections.

In the surgical suite, the operative area should be scrubbed for 3–5 min with iodophore soap. Numerous studies have indicated that the traditional 10-min scrub is not necessary. The area should be scrubbed not with vigor but with thoroughness. If one presses hard on the skin it produces a local inflammatory response which, on cutting the skin, leads to numerous bleeders in the superficial area of the incision. This in turn leads to either postoperative hematomas or to increased amounts of foreign material in the wound in the way of sutures or cauterized tissue. If the patient is impregnated with dirt and grease, this should be removed well before the actual operation. The soap should be removed and the

area painted with an iodophor solution, which is left to dry. Povidone-iodine acts relatively quickly but requires several minutes to achieve its local bactericidal effect, so it must be left in place and not wiped away. Placing plastic sheets over the exposed skin does not prevent infection but we find them practical to use since they hold towels in place without clips and keep the towels under them dry. If the patient has a stoma in the intra-abdominal wall, such as a urinary conduit or colostomy, the plastic adhesive drape is placed so as to exclude the stoma from the incision.

Good technique

The incision should be cleanly made and should be carried down to the fascia quickly in one line without terracing. It is unwise to clean off the fascial layers since

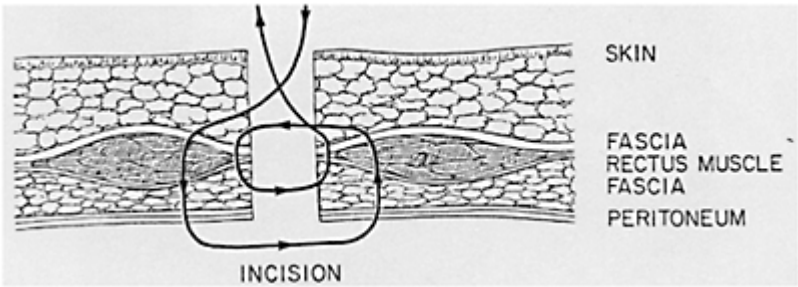

Figure 78.7 Smead-Jones one-layer with wire or monofilament nylon closure

this will greatly decrease the blood supply to the fascia. Bleeders should be appropriately clamped and tied or cauterized, using delicate technique. It is our preference to use a clamp on the vessel and a polyglycolic acid suture tie. Once the abdomen is open we suture towels to the peritoneum and the fascia so that the wound is excluded from the operative area. Using adhesive tapes rather than sutures to close the skin does not alter the infection rate and often results in a wider scar.

In contaminated cases it is best to close the fascia and peritoneum with either nylon or stainless steel sutures. If sutures are put in the subcutaneous tissue, polyglycolic acid suture should be used as this is the least reactive material. No free space should be left in the incision. In patients who have pulmonary or cardiac problems, are malnourished, or are expected to show a prolonged recovery phase with ileus, it is wise to use a running mass closure with permanent sutures. We have found through experience that the retention suture that comes to the outside leads to many infections. Over the last 8 years we have used the Smead-Jones far-and-near closure (Figure 78.7) and have had no eviscerations. We feel that this technique leads to fewer infections and gives a strong, permanent closure.

In heavily contaminated cases with abscesses or peritonitis, and where there is bowel surgery with fecal spillage, it is best to close the anterior abdominal fascia and the

peritoneum with Smead-Jones sutures and leave the skin open (Table 78.4). At some time between the

Table 78.4 Correlation of wound classification system for elective surgical cases and corresponding reported wound-infection rates for penetrating abdominal wound and bite wounds

Wound classification	*Risk of postoperative wound infection*
Clear	1–3%
Clear-contaminated	7–10%
Contaminated	20–25%
Dirty	40%

Adapted from the National Research Council.
Weigelt JA. *Infect Dis Clin Pract* 1996; 5:S92–5

fourth and the sixth day, the skin can then be closed with previously placed sutures, a procedure done on the ward under local anesthesia. Rarely do these secondarily closed wounds become infected, and the postoperative stay is not prolonged.

The cosmetic result is as good as in those cases closed primarily. A study of delayed primary wound closure in Canada indicated that the authors decreased their wound infection rate from 24% to 3% by leaving the wound open and closing it on the fourth day. Other studies have confirmed these results. If fewer than 105 bacteria per gram of tissue are found in the open wound, the wound, when closed secondarily, will heal 98% of the time. If the bacterial contamination is greater than this, the infection rate is much higher. However, most of us are not able to do bacterial counts

Table 78.5 Tetanus prophylaxis guidelines

Situation	*Recommendations*
Clean, minor wounds:	
No prior history of tetanus immunization	Primary immunization consisting of two doses (0.5 ml each) of tetanus (combined tetanus/diphtheria toxoid) vaccine intramuscularly four weeks apart followed by a third dose 6 to 12 months later.
Prior tetanus immunization, but >10 years	Tetanus vaccine booster (0.5 ml) intramuscularly
Prior tetanus immunization <3 years	Optional
Status unknown	Primary vaccinations (three doses)
All wounds contaminated with dirt, feces, soil, saliva,	Combined tetanus and diphtheria toxoids absorbed PLUS

punctures, crush, burns or frostbite	Tetanus immune globulin (TIG) 200 IU intramuscularly. TIG provides immediate immunity for 25–28 days during which time the patient is developing active immunity. Injection should be given at a separate site.

Modified from *MMWR* 1985; 34:405–14, 419–26

and depend on the time and the appearance of the wound; generally by the fourth or fifth day the surface granulations are healthy and delayed closure is possible.

PROPHYLACTIC MEASURES FOR INJURIES AND WOUNDS

Management of traumatic wounds involves three major principles:

(1) immediate wound care;
(2) evaluation of the need for prophylactic antibiotic therapy; and
(3) evaluation of the need for prophylactic vaccination.

Immediate wound care

Therapy begins with careful cleansing of the wound in order to remove any organic contamination created by abrasion, deep puncture or bite wound injury. Sterile saline followed by use of hydrogen peroxide coupled with debridement of any necrotic tissue and documented hemostasis achieves the first level of care. When evaluating a wound which occurred at a time more remote, careful examination for pus, foreign bodies or the presence of gas in the adjacent tissues is imperative.

Antibiotic therapy

Prophylactic antibiotic therapy is usually advocated in the following conditions:

(1) heavily contaminated wounds;
(2) cat bites;
(3) human bites; and
(4) wounds in diabetic or immunocompromised individuals.

A combination of beta-lactam antibiotic such as amoxicillin/clavulanate (Augmentin) 250–500 mg q 8h for 3–5 days and a fluoroquinolone with extended anaerobic coverage is effective prophylactically. Greater anaerobic coverage is required when dealing with supportive or dirty wounds. If there is any evidence of a systemic response such as fever, tachycardia, cellulitis/lymphangitis or fasciitis, systemic antibiotic therapy becomes the standard of care. If a puncture wound results from a nail or similar object going through the bottom of a sneaker, coverage against *Pseudomonas aeruginosa* is mandatory. *P. aeruginosa* colonizes the inner layers of athletic shoes. The presence of gas in adjacent tissue should alert the clinician to the possibility of clostridial infection. In diabetics and patients with vascular insufficiency, selected *Enterobacteriaceae* such as *Escherichia* may produce this phenomenon.

Prophylactic vaccination

Tetanus prophylaxis must be considered in all wound cases. the recommended guidelines for the administration of tetanus toxoids and tetanus immune globulin are listed in Table 78.5.

Factors increasing probability include active infection at the operative site, fecal contamination, site of fecal contamination, presence or absence of shock, hemostasis.

In cases of fecal contamination of operative site, prophylactic antibiotic combinations that did not include anaerobic coverage resulted in greater than 20% wound infection rates, whereas rates of 10–14% were documented when the antibiotic coverage effectively included anaerobic agents. Studies with cefoxitin, cefotetan or ampicillin/sulbactam have documented infection rates of approximately 10% or less.

Should bowel penetration involve the stomach or small bowel due to the shift toward class I antibiotic coverage and particularly the *Enterobacteriaceae,* consideration should be given to use of a prophylactic combination whose primary coverage encompasses both the anaerobic spectrum of bacteria and the *Enterobacteriaceae,* e.g. trovofloxacin, clinofloxacin, clindamycin/aminoglycoside. Timing of dosing is critical. Tissue levels need to be established and in optimal range at the time of surgery. Redosing is currently based on the known antibiotic half-life, however consideration should be given to fluid volume distribution and blood loss.

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APPENDIX I
Collection and handling of bacteriological and viral obstetrics and gynecology specimens

DIRECT EXAMINATION

Gram stains

The Gram stain is used to determine morphological bacterial types, aid in the selection of culture media, and assess specimen quality (Table A I.1). Smears should be examined for both microorganisms and cells. It is important to assess the morphology and quantity of microorganisms present. Microorganisms are seen on smears only if present in the specimen at a concentration of $\geq 10^4$ organisms per ml.

The character and relative quantity of epithelial cells and leukocytes should be determined. The presence of leukocytes generally indicates a good quality specimen has been obtained from the area of inflammation. The presence of squamous epithelial cells in sputa and other specimens correlates with a poor quality specimen. Squamous epithelial cells should not be confused with ciliated epithelial cells. In the case of a sputum sample, the latter cells indicate the specimen is of a lower respiratory tract origin.

Some bacteria do not stain well with the Gram stain and require tissue stains like the Giemsa/Wright stain (for *Calymmatobacterium granulomatis, Borrelia, Rickettsia,* and *Chlamydia*) or Giemsa (for *Rickettsia, Chlamydia* and *Legionella pneumophila*). The physician must indicate to the microbiologist the possibility that one or more of these agents may be present in order to assure proper staining of the specimen.

Table A I.1 Bacteriological specimens which require concomitant Gram staining

Sputum
Abscess material
Infected peritoneal fluid
Endocervical/endometrial cultures
Cerebrospinal fluid
Other body fluids (except urine)

Gram-staining of cerebrospinal fluid (CSF)

Gram stain analysis of even clear CSF is indicated in the face of clinical evidence of meningitis. In very early cases of bacterial meningitis, and in fungal meningitis, the cell count may be normal despite a positive culture. Because the number of microorganisms present in infected CSF tends to be small, some procedure for concentration of any organism present needs to be performed. A turbid specimen can be centrifuged at 2500 rpm for 15–30 minutes and the sediment can be used both for smear and culture purposes. Careful examination of the Gram-stained smear under oil immersion is frequently necessary. An alternate method is to concentrate the specimen by cytocentrifugation.

When fungal meningitis is suspected, a cryptococcal antigen detection test should be ordered on the CSF.

Gram-staining of other fluids

The percutaneous aspiration of pleural, pericardial, peritoneal and synovial fluids must be performed under aseptic conditions. Gram stain smears of the centrifuged sediment of clear or slightly clouded fluid are necessary.

Gram-staining technique

The thinly smeared sample should be allowed to dry, and is then gently heat-fixed by passing it quickly over a Bunsen burner flame or microbiologic incinerator a few times. The slide should be hand-held and not allowed to become more than warm to the touch. Excessive heating will lead to a disruption of cellular elements and may sometimes obscure microorganisms by causing clumping of proteinaceous material. Then, while holding the slide over a sink with a soft flow of tap water, the staining reagents are added in the following fashion:

(1) Crystal violet: cover the smear and swirl gently for a few seconds, then pour off and wash in tap water.
(2) Gram's iodine: same procedure as for crystal violet then rinse gently with water.
(3) Decolorizer: carefully cover the smear while holding it horizontally and allow blue stain to elute for a second or two. Then tilt it gently and continue to add decolorizer. As the blue begins to fade noticeably, wash quickly but gently in water. In a thinly smeared sample, approximately 3–5 seconds is adequate, using acetone-alcohol decolorizer. This step is most critical and requires careful attention.
(4) Safranin: same procedure as for crystal violet. After pouring off the counter-stain (safranin), wash gently with water. Then blot the slide carefully between clean filter paper and allow it to air-dry before microscopic examination. Residual moisture may interfere with oil-immersion microscopy.

BACTERIOLOGICAL CULTURES

Skin cultures

Abscesses

Material from a previously undrained wound abscess should be aspirated with a needle and syringe after appropriate decontamination of the overlying skin. Fluid thus obtained should be forwarded to the microbiological facility in a needleless, capped syringe with all of the air expressed out, or in an anaerobic transport vial (see section on anaerobic cultures, below).

Sinus tracts

Sinus tracts usually originate in bone or in lymph nodes. The orifice of the tract should be cleansed thoroughly with a suitable antiseptic, then curettings of the tract's lining should be taken as close to its base as possible.

Ulcers

Ulcers should be carefully debrided and proper samples collected from the base or progressive edge where bacteria actively multiply. Unremoved crust or surface pus should not be collected since it is often contaminated by other bacteria, thus not reflecting the true infecting flora.

Vesiculopustules

This type of lesion should be unroofed with a sterile needle before obtaining the specimen. Rub the base of the lesion with a dacron swab to obtain cellular material. For viral cultures, place the swab in a transport media. A touch preparation should also be made using a separate swab and clean microscope slide (see viral cultures).

Anaerobic cultures

Specimen collection and transport

Good anaerobic bacteriology starts with proper collection of the specimen (Table A 1.2).

Sites normally inhabited by a rich indigenous flora, such as the intestinal tract or vagina, should not be sampled for anaerobes except under special circumstances and in special ways (e.g. for quantitative study of upper small bowel flora in the blind loop syndrome) or should be done using specialized techniques which minimize contamination from the sites to be sampled. Use of a double lumen catheter, bronchial brushings, and

bronchoalveolar lavage fluid allow the lower respiratory tract to be sampled. An endometrial suction curette biopsy can be used to obtain endometrial samples.

Table A I.2 Acceptable specimens for anaerobic culture

(1)	Normally sterile fluids (i.e. blood)
(2)	Normally sterile area (i.e. peritoneal and pleural cavities)
(3)	Deep abscesses
(4)	Deep aspiration of wounds and tissue specimens
(5)	Transtracheal, cul-de-sac aspirates

Specimen selection

Good anaerobic bacteriology is time-consuming and expensive. Therefore, it is important that only specimens which have been selected and collected properly be submitted for anaerobic culture. A poor specimen will not only give useless or misleading results, but will also prevent the laboratory personnel from devoting sufficient attention to valid specimens.

Pus, when present, is best aspirated into a syringe through a needle and injected into an anaerobic (oxygen-free) transport vial containing an oxidation-reduction indicator. Great care must be taken to exclude air. Even transient contact with molecular oxygen is as lethal as an autoclave for strict anaerobes. Syringes used for aspiration should not be used as transporters (with the needles attached) because of the potential danger of needle stick injuries. Anaerobic vials are commercially available from several manufacturers.

In selected instances, (i.e. ruptured tubo-ovarian abscess or gangrenous wound infections), it is not possible to obtain a specimen for bacteriological analysis by aspiration. In these circumstances, **pieces of infected tissue** obtained by excision or biopsy are best transported in loosely capped containers sealed in anaerobic gas-impermeable bags.

Conditions of transport do affect the viability and/or relative proportions of bacteria present. Rapid delivery at room temperature is best for transportation of specimens. Oxygen diffuses better at lower temperatures. The gross appearance (purulence, necrotic tissue) and odor of the specimen can give the laboratory valuable clues to the presence of anaerobes.

Gram stain for anaerobic infections

Next to the physician’s ability to anticipate when the anaerobic infection is present on clinical grounds, the

Table A I.3 Probability of documenting bacteremia with increasing numbers of blood culture

Percentage of bacteremia detected	*Number of 20 ml blood cultures*
80	1
88	2
99	3

Washington J-II. *Mayo Clinic Proc* 1975; 50:91

most important diagnostic tool is the Gram stain. When dealing with a well-established abscess, the ocularcerebral reflex is almost as accurate as an anaerobic diagnostic facility. **Whenever you take an anaerobic culture, make a Gram stain!**

The morphotypes and relative quantities of both the host and bacterial cells present in the preparation will provide information on the specimen quality and may give clues to the presence of particular bacterial species and suggest the need for special selective media (Table A 1.3). Furthermore, the Gram stain information also provides quality control for specimen transport and isolation efficiency.

Blood cultures

Site selection and preparation

Venipuncture sites involved with dermatologic disease will often yield a higher rate of contamination. Arterial blood provides no higher yield than does venous blood.

Site preparation for the withdrawal of blood is one of the most important aspects of culturing blood for bacterial pathogens. The recommended procedure involves decontamination with 70% isopropyl or ethyl alcohol for one minute followed by povidone iodine for one minute. If the patient exhibits or has a known allergy to iodine, only 70% alcohol should be used.

The antiseptic solution is applied concentrically, starting at the center. The disinfectant should be allowed to dry completely before the vein is punctured. After disinfection, the vein should not be repalpated. Sterile gloves should be used throughout this process, in accordance with current infection-control guidelines for universal precautions. The site should be prepared with a double applicator of alcohol. Do not change the needle after venipuncture and before inoculation of blood into the culture media. Intravascular catheters are most acceptable as alternatives to cutaneous venipuncture.

Volume of blood per culture

One of the most important variables in the detection of bacteremia is the volume of blood cultured. Ten milliliters is the minimum volume that should be collected. Collecting 20 ml or 30 ml of blood increases the yield of isolates over 25% and 50% respectively. Because the magnitude of bacteremia is greater in children than in adults, cultures of 1–5

ml are reasonable. Blood contains complement antibodies and enzymes which are potentially bactericidal.

To counter these naturally occurring systems, a blood to broth ratio of 1:5–1:10 should be achieved. In addition, most commercial blood culture broths contain sodium polyanetholsulfonate which neutralizes the antibacterial activity of blood.

Never divide a single sample into multiple sets of blood cultures. In other words, each blood sample drawn equals one blood culture (one aerobic and one anaerobic bottle).

As shown in Table A I.3, the percent of bacteremias detected is optimal if three separate blood cultures are obtained. A single blood culture lacks sensitivity (80%) and thus should be avoided. On the other hand, more than three blood cultures adds little to the sensitivity and should also be avoided.

Situations requiring multiple blood cultures

Multiple blood cultures are rarely cost-effective with the following exceptions:

(1) Critically ill patients with sepsis;
(2) Immunocompromised individuals with suspected infectious complications;
(3) Patients with fever of unknown etiology; and
(4) Patients suspected of having:

(a) osteomyelitis
(b) infectious endocarditis;

Limitations of blood culture

No single medium is optimal for all pathogens. Bacteria requiring special media and/or processing include:

• *Actinobacillus*
• *Brucella*
• *Bartonella*
• Nutritional variant streptococci
• *Legionella*

Types of blood culture bottles

A routine blood culture involves the use of two blood culture bottles (referred to as a set). One is used for aerobic blood culturing, the other for anaerobic blood culturing. There are a number of different types and brands available.

If antibiotic therapy has already been initiated prior to collection of the blood specimen, this diminishes the probability of obtaining an isolate, but does not totally invalidate the culture. Some blood culture bottles contain antibiotic removal resins. These non-specifically bind and remove many antibiotics.

In some instances, the physician may suspect an L-form or cell-wall deficient organism. The blood culture bottle containing a hypertonic medium with 10% sucrose should be used in these cases.

Timing and spacing of blood cultures

There are little data on the optimal time to collect blood for culture in humans. Animal data suggest that the optimal time for collection of blood for culture is immediately prior to a fever spike. Since this is somewhat impractical, it is generally recommended that blood be collected at the fever spike. The spacing of blood cultures is somewhat dependent upon the clinical situation and the need to initiate antimicrobial therapy. When possible, separate blood cultures should be spaced 30–60 minutes apart and should be collected before the initiation of antibiotic therapy.

Urine cultures

Obtain early morning specimens whenever possible. Bacterial counts will be higher at this time. Care must be taken to avoid contamination of the specimen with organisms from perineum, distal urethra, vaginal secretions, hands, skin, and clothing. Cleansing procedures must remove contaminating organisms from the vulva, urethral meatus, and perineal area.

Urine must be obtained properly, and transported and processed as soon as possible. No more than one hour should elapse between specimen collection and incubation. If this time schedule cannot be followed, the urine specimen must be refrigerated immediately.

Endocervical and mucosal cultures for *Neisseria gonorrhoeae*

The principal reason for obtaining an endocervical culture is to exclude the presence of *Neisseria gonorrhoeae* (Table A I.4). If a culture is to be performed, it should be obtained before any other procedures.

In obtaining bacteriological specimens for identification, it is important to moisten the speculum only with warm water. Do not use any other lubricants as the majority of lubricants have been shown to be partially bacteriocidal for *Neisseria gonorrhoeae* and may mask detection of occult infection.

(1) Never culture a specimen on a plate which is not at least at room temperature. *Neisseria gonorrhoeae* has an extremely limited thermal tolerance. Preferential growth occurs between 30 and 38ºC. Temperatures below room temperature will rarely sustain the replication of *Neisseria gonorrhoeae* and often account for non-recovery of the organism.
(2) Incubate cultures immediately. Again, the thermal lability of the organism is such that maintaining cultures at room temperature for more than one hour will have a deleterious effect.
(3) Be sure to provide a source of carbon dioxide. In dealing with the Thayer-Martin or Martin-Lewis plates, it is imperative that they not only be incubated, but that candle jars be utilized to provide the critical 5% CO_2 atmosphere required for the initiation of bacterial replication. The Neigon (JEMBEC)

Table A I.4 Do's and dont's of culturing for *Neisseria gonorrhoeae*

(1) Never inoculate a culture plate which is not at least at room temperature.

(2) Be sure to roll (not merely streak) a cotton swab in a 'Z or 'W' pattern.

(3) Assure a source of CO_2

- JEMBEC uses a $NaHCO_3$ tablet.
- modified Thayer Martin method uses a candle jar or a CO_2 incubator.

(4) Be sure to incubate 12–18 hours before transporting to a diagnostic facility.

system carries its own CO_2-generating capacity, such that the use of candle jars is superfluous.

(4) *Neisseria gonorrhoeae* is extremely temperature liable and will not grow, or does so only poorly, on culture plates recently taken from the ice box.

Probably the single greatest factor contributing to falsely negative cultures is the failure of the physician to roll the swab in a 'Z' or 'W' manner. The endocervical swab samples 360 degrees, yet if the swab is not rolled on the culture medium, a maximum of only 33–50% of the swab sample is obtained. Total (100%) sampling is especially important when *Neisseria gonorrhoeae* is present in quantities which are numerically reduced, (e.g. the asymptomatic carrier or the patient with initial gonococcal salpingitis that is now undergoing a competitive elimination of *Neisseria gonorrhoeae* at the endocervix).

LABORATORY DETECTION OF VIRUSES

The selection of tissue culture lines for inoculation is based on:

(1) source of specimen;
(2) clinical diagnosis; and
(3) availability to the testing facility.

The number of infectious particles and the temperature of incubation in an appropriate culture line are the prime determinants of how quickly cytopathic effects will be observed.

Table A I.5 Recommendations for collection of specimens for isolation of viruses

Vesicles/pustules: Rupture vesicles or pustules with a sterile needle and proceed as follows:

Ulcers:

(1) Vigorously touch the underlying ulcer with a dacron swab.*

(2) Place the swab in an unfrozen viral transport media.

(3) Confirm all patient care data for label.

(4)	Place the viral transport at 4ºC as quickly as possible. If the culture cannot be inoculated into appropriate tissue culture lines within 72 hours, freeze specimen at −60ºC.

*A swab gently touched on a lesion collects a small fraction of the virus present, compared to a firm and complete rolling of the swab.

Virus isolation

Media

A number of viral transport media are available. The media can be kept at 4ºC for two weeks (and several months if kept frozen). When using frozen transport media, the media need to adequately thaw prior to insertion of the dacron tipped swab.

Specimen handling and storage

The specimen should be maintained at 4ºC until it can be inoculated onto an appropriate tissue culture line. Most cultures remain stable in transport media at 4ºC for periods of 48–72 hours. Freezing a specimen, even at −60ºC, will result in a reduction in the number of infectious viral particles present.

Rapid diagnosis of herpetic lesions

If a rapid diagnosis is required, in the case of a suspected herpetic lesion from a neonate, (or in a case of suspected chickenpox or zoster), a direct smear of the lesion should be made. Carefully clean the outer surface of the vesicle with an alcohol wipe and allow to dry. Unroof the vesicle with a sterile needle (vesicular fluid may be collected for culture). Collect cells at the base of the lesion by rubbing vigorously with a sterile dacron swab or scrape gently with a scalpel. Rub the swab or scalpel scrapings evenly over three areas on a clean microscope slide. Allow to dry and transport to laboratory. Do not fix with cytology fixative.

Table A I.6 Specimen collection for *Chlamydia* cultures

A. Acceptable specimens:

Disease	**Specimen**
Urethritis	urethral swab
Cervicitis	endocervical swab
Conjunctivitis	conjuctival swab
Trachoma	conjuctival swab
Infant pneumonitis	nasopharyngeal swab
Lymphogranuloma venereum[1]	bubo aspirate

Fitz-Hugh-Curtis syndrome (perihepatitis)	peritoneal fluid, endocervical swab
Pelvic inflammatory disease (PID)	peritoneal fluid, tissue, endocervical swab
Psittacosis[1]	sputum, lung tissue
Pneumonitis, upper respiratory tract infection of adults' and older children	nasopharyngeal or throat swab, endotracheal aspirate or wash, bronchoalveolar lavage fluid, lung tissue
Sexual abuse (prepubescent female)	vaginal, rectal, throat, urethral swab
Sexual abuse (male)	rectal, throat, urethral swab
B. Unacceptable specimens:	
•	Saliva
•	Semen
•	Urine
•	Blood
•	Vaginal specimens (except for prepubescent females or women with a previous history of hysterectomy)
C. Specimen collection:	
(1)	Collect swab specimens using a dacron tipped plastic shafted swab. Do not use wooden shaft swabs or calgiswabs, as they are toxic to the chlamydia.
(2)	After collection, place the swab in a thawed tube of chlamydia transport media, cut the plastic shaft leaving the swab in the tube, and recap the tube.
(3)	Other specimens, such as tissue and fluids can be added directly to a tube of chlamydia transport media.
(4)	Place the specimen in a water-crushed ice bath (wet ice), at 4ºC.
(5)	Transport to the laboratory on wet ice.

Notes: [1]Serum for acute and convalescent titers should be collected for diagnosis of lymphogranuloma venereum, psittacosis, and *Chlamydia pneumoniae* infections.

Order a direct immunoflourescent antibody test for Herpes simplex virus and/or varicella-zoster virus. Because of its low sensitivity, specificity and inability to distinguish between HSV-1, HSV-2, and VZV, a Tzanck smear should be avoided.

Table A I.7 Specimen collection for *Chlamydia* DNA and/or *Neisseria gonorrhoeae* DNA probe tests

A. For specimen collection use only the Gen-Probe collection swabs

B. Urethral specimens:

(1) The patient should not have urinated for at least one hour prior to sampling.

(2) Insert the male swab into urethra and rotate for 3–5 seconds.

(3) Immediately insert swab into the Gen-Probe transport tube.

(4) Transport as soon as possible to the microbiology laboratory.

C. Endocervical specimens:

(1) Remove mucus from the exocervix with one of the large swabs. Discard the swab.

(2) Rotate the second large swab in the endocer vix 15–30 seconds. Avoid touching the vaginal walls when inserting and removing the swab.

(3) Immediately insert swab into the Gen-Probe transport tube.

(4) Transport as soon as possible to the microbiology laboratory.

D. Conjunctival specimens (for *Chlamydia* DNA test ONLY):

(1) Using the male swab, firmly stroke the lower conjunctiva 2–3 times.

(2) Immediately insert swab into the Gen-Probe transport tube.

(3) Transport as soon as possible to the microbiology laboratory.

E. *Chlamydia* DNA specimens are not acceptable from suspected cases of sexual assault or abuse.

Cultures

The herpes viruses grow easily in a variety of tissue culture lines. Cytopathic effect is usually observed within 24–72 hours of inoculation, although negative cultures are generally held for up to seven days before a final report is issued. Diagnostic confirmation requires fluorescent antibody staining of virus infected cells by monoclonal antibodies to that virus.

Cytomegaloviruses

Cytological techniques

The cytomegaloviruses cause cytoplasmatic giantism. This finding coupled with the presence of a single large Fuelgen-positive intranuclear inclusion body is highly suggestive. Urine specimens for cytology should have a high specific gravity, (e.g. early morning specimens).

APPENDIX II

Diagnosis and therapy of genitoulcerative disease

VULVAR ULCERS OF POSSIBLE INFECTIOUS ETIOLOGY

Perhaps one of the most challenging problems confronting the obstetrician-gynecologist is obtaining the ultimate diagnosis in a patient with a vulvar ulcer. The frequency with which infectious agents produce such a lesion and the multiplicity of etiologies necessitate the clear cut delineation of pragmatic steps which will lead to the ultimate diagnosis in most instances.

Physical examination

When confronted with a lesion for which the diagnosis is in doubt, a defined procedure is helpful.

(1) Draw a diagram of the lesion and its relationship to the surrounding architecture. At this time note the number of lesions and determine whether the lesion is in the field of inguinal lymphatic drainage or in that of the anorectal lymph nodes.

Example:

(2) Carefully examine the margin and base of the lesion (a cut-edge diagram is often helpful in determining whether the edges are heaped up and rolled, well-defined, shaggy, undermined, etc.). Record the character of the exudate.
(3) Note the presence of pain.
(4) Determine the presence of adenopathy.
(5) Record any associated clinical features.

By utilizing this stepwise procedure, one has not only defined the characteristics of the lesions, but also availed oneself of certain broad categories that have a relatively specific differential diagnosis. Painless lesions or lesions with well-defined margins have distinct differential diagnoses (Table A II.1).

Diagnostic procedures

Following careful physical examination and graphic delineation of the lesion:

Table A II.1 Differential diagnosis of vulvar ulcers

Pathogen	***Lesions***	***Pain***	***Characteristics of lesion***	***Clinical features***	***Diagnostic procedure***
Herpes simplex types 1 & 2 or multiple	Single	Yes	Vesiculopustules; shallow ulcers with secondary infection		Virus isolation (any tissue culture line)
Vaccinia virus	Single or multiple	Yes	Vesiculopustules; shallow ulcers with secondary infection	History of recent vaccination or intimate contact with recently vaccinated person; VDRL may be +, but FTA −	Virus isolation (any tissue culture line)
Behcet's syndrome (causative agent unknown)	Multiple	Yes	Shallow-based ulcers with secondary infection	Concomitant oral apthous lesions; possible uveitis or iridocyclitis	None
Treponema pallidum (syphilis)	Single	No	WELL-DEFINED MARGINS, rolled; clean	Tender inguinal adenopathy	Darkfield examination or VDRL and FTA
Chlamydia trachomatis (lymphomogranuloma venereum)	Single	No	Granular base; shallow ulcer with secondary infection	Anorectal proctitis possible	Complement fixation F test or Frei intradermal skin test for LGV
Squamous cell carcinoma	Single	No	Firm lesion with rolled margins		Biopsy
Mycobacterium tuberculosis	Single	No	Well defined borders; granular base	Systemic disease; PPD +	Culture; touch prep or biopsy with Zieh-Neelsen staining
Calymmatobacterium (Donovania) granulomatis (donovanosis)	Single; may be several	Yes	Well defined borders; clean, granular base	Inguinal adenopathy; pseudobubo formation	Donovan bodies; touch prep of lesion or biopsy
Hemophilus ducreyi (chancroid)	Single	Yes	Shaggy borders surrounding necrotic exudate		Culture; response to therapy

Entamoeba histolytica (amebiasis)	Single	Yes	Shaggy undermined edges, exudate similar to 'anchovy paste'	Possible history or presence of acute diarrhea	Amebas on touch prep biopsy
Trauma with secondary bacterial infection	Pattern of involvement depends on bacterial pathogens				
a) Microaerophilic B-streptococci and coagulase+ staphylococci (Meleney's ulcer type II)	Single	Yes		Fulminating pattern of spread and tissue destruction	Culture
b) Bacteroides (Anaerobic organism)	Single	Yes	Ulcer with underlying abscess	Deep traumatic penetration with foul-smelling exudate	Culture

Table A II.2 Value of diagnostic procedures for specific organisms

Pathogen	***Touch preparation and darkfield examination***	***Biosey***	***Culturing or serologic analysis***
Herpes simplex virus	Multinucleated giant cells with intranuclear clear inclusion bodies	Intranuclear inclusion bodies in parabasilar cells of epidermis	Virologic culture
Vaccinia virus	Intracytoplasmic inclusion bodies	Intracytoplasmic inclusion bodies	Virologic culture
Behcet's syndrome	—	—	—
Treponema pallidum	Motile spirochetes demonstrable on darkfield examination of tissue transudate	Mixed plasmacytic-lymphocytic infiltrate with small-vessel endarteritis; using silver-impregnated Levaditi stain, spirochetes may demonstrate	VDRL & FTA-ABS tests may be +
Chlamydia trachomatis (Lymphogranuloma venereum)	—	Central necrosis surrounded by epithelial cells and infected granulation tissue	Diagnosis inferred from CF antibody titer of 1:40 or higher, or + Frei test with 1 cm papule in 48–72 h
Squamous cell carcinoma	Diagnosis suggested by cytologic atypia	Definitive diagnosis based on histopathology	—
Mycobacterium	Demonstrable with	Diagnosis inferred on	Negative PPD aids

tuberculosis	Ziehl-Neelsen staining	finding epithelial and Langhans giant cells	in excluding diagnosis Culture
Calymmatobacterium (Donovania) granulomatis	Donovan bodies with macrophages	Donovan bodies within macrophages	—
Haemophilus ducreyi	'School of Fish' pattern	—	Bacteriologic culture
Entamoeba histolytica	Trophozoites on wet mounts	Trophozoites with PAS stain	—
Secondary bacterial infections	Gram-staining may give presumptive diagnosis	—	Bacteriologic culture

(1) The most useful diagnostic procedure is direct examination of the exudate or transudate taken from such a lesion (Table A II.2), for example, touch preparations, cytologic smears, and wet mounted preparations (darkfield examination where indicated) are an integral part of the initial differential. Example: motile spirochetes on dark-field examination.
(2) Biopsy of the margin and a portion of the base of the lesion is probably the second most valuable diagnostic procedure, after microscopic observation, in establishing a definite diagnosis. Example: plasmacytic lymphocytic infiltrate; spirochetes demonstrable with Levaditi stain.
(3) Culturing for bacteria, mycobacteria, viruses, and protozoa is often a costly procedure with a low yield unless indicated on clinical or histologic grounds. Suspicion of one sexually transmitted disease should intensify monitoring for second agent at other sites.
(4) In certain instances such as lymphogranuloma venereum additional procedures may be necessary. The diagnostic work-up for the individual organisms listed in Table AII-1 is described in Table A II-2.

The procedures listed should all be performed at the same visit.

GRANULOMA INGUINALE *(CALYMMATOBACTERIUM GRANULOMATIS)*

Granuloma inguinale is a disease due to an intracellular Gram-negative rod, *Calymmatobacterium granulomatis,* which is usually endemic in areas with both high temperatures and humidity. In the United States, disease occurs primarily in port cities in the southern part of the United States.

The disease is apparently not very contagious while a significant mode of transmission involves sexual contact. Disease does not invariably affect conjugal partners despite repeated contact.

Natural history of the disease

The predilection of lesions for the genital areas and the occasional occurrence of disease in sexual partners of infected individuals constitute the prime evidence to support the concept of granuloma inguinale as a venereal disease.

The prevalence of the disease among pederasts and the predominant anal and perianal predilection of the lesions strongly suggest that rectal coitus is the prime means of transmission of infection, either by contamination of the skin directly through anal intercourse (whether it be heterosexual or homosexual) or indirectly by faulty hygiene. Further evidence supporting the inferred thesis of venereal disease transfer, secondary to rectal coitus, can be drawn from the observations that the disease process is infrequent among prostitutes. In the preantibiotic era, individuals in the florid stage of the disease only occasionally transmitted infection to their sexual partners. From clinical studies, an incubation period of 17.4 days has been calculated; however, experimental infection of human volunteers has produced disease in 50 days.

The disease is only mildly contagious. In most cases lesions cannot be demonstrated in sexual consorts. Evidence of infection as opposed to disease is detected in 12–52% of marital or steady sexual partners.

The common sites for lesions, in women, are the labia minora, fourchette, and labia majora. The perianal region also can be affected. Bedi has reported an unusual case of non-venereal transmission of perianal granuloma inguinale in a child. Another site that may occasionally be affected by this disease is the oral cavity.

The initial lesion usually begins as a reddish brown, flat-topped papule which often spreads and then ulcerates in the center. Not infrequently, other papules appear at about the same time. When they ulcerate, the lesions eventually coalesce.

The ulcer may show variation in its morphology:

(1) The ulcerative or ulcerogranulomatous form—the fleshy, exuberant lesion—presents as a beefy-red granulomatous ulcer, usually single, which is nontender, non-indurated, and bleeds profusely on touch;
(2) The hypertrophic or verrucous form consists of an ulcer or growth with a raised, irregular edge or surface, drier than the ulcerative variety, with an elevated, granulomatous base;
(3) The necrotic type gives rise to extensive destruction of genitalia with profuse, foul-smelling exudate; and
(4) The sclerotic or cicatrical variety presents as a band-like scar in and around the genitalia.

As a rule, the ulcer tends to have a clean base composed of fresh granulation tissue and to have well-defined borders. The advancing edge of the lesion exhibits a scrolled appearance owing to epithelial hyperplasia and acanthosis of the squamous epithelium. The degree of hyperplasia (and not infrequently dysplasia) in response to infection may cause an erroneous diagnosis of low-grade squamous cell carcinoma.

Spread of the disease may be by contiguous contact, autoinoculation, or lymphatic extension. The histologic demonstration of lymph node involvement and the development of pseudobubo in males stress the role of lymphatic dissemination from the superficial

genital lesion. In females, the regional lymph nodes enlarge somewhat and are occasionally tender, but they do not suppurate unless gross secondary infection of the initial lesion is present.

Biopsy of the initial lesion reveals, in addition to the secondary epithelial change, a granulomatous proliferative response and a secondary connective tissue attempt at repair. The histopathologic feature of the ulcer of donovanosis is that of a dense granulomatous tissue reaction consisting mainly of small lymphocytes, with a scattering of the typically large mononuclear cells which may contain the pathognomonic Donovan bodies. Small collections of polymorphonuclear neutrophils (micro-abscesses) secondary to superimposed bacterial infection are typical. In the absence of secondary infection, neutrophils are conspicuously absent. Within the granulation tissue the capillaries tend to be prominent, owing to reactive hyperplasia of their endothelial cells. Even in the absence of Donovan bodies, the histopathology of infection due to *C. granulomatis* is sufficiently characteristic to warrant a presumptive diagnosis.

The more advanced lesions represent a composite of the two processes of exuberant granulomatous proliferation and fibroblastic repair. With partial resolution of infection, isolated foci of plasma cells and lymphocytes appear, as well as occasional macrophages within the interstices of connective tissue. With arrest of the disease process, the granulation tissue is replaced by newly grown connective tissue.

One of the less commonly seen features of the disease is a gross local swelling of the affected area. It may develop before treatment or during the phase when the ulcers are healing. These hard, knobby swellings are due to obliteration of predominantly efferent lymphatics. Biopsy of such a lesion reveals grossly dilated lymphatics.

With secondary infection of the initial ulcers, the gross appearance of the lesions changes, owing to extension of the area of ulceration deep into the underlying dermis with excavation and undermining of the margins. With appropriate therapy, the fibroblastic component predominates, leaving scar formation as the end-stage lesion of genital involvement. In 6% of the cases, extragenital lesions are observed. Metastatic hematogenous infection as well as involvement of the oral cavity has been described. The infection, particularly after delivery or abortion, infrequently extends from the cervix and may involve the uterus, fallopian tubes, and ovaries.

With extensive disease and secondary infection, systemic signs such as fever, anemia, weight loss, malaise, and leukocytosis may occur. Although the diagnosis may be inferred because of the clinical presentation and the exclusion of other disease processes, a definitive diagnosis is still contingent upon the demonstration of Donovan bodies.

Some of the lesions being separate, other confluent. The margin of the lesion is raised and scrolled, and the base is granular and covered imperfectly by a thin gray slough.

Diagnosis

Many clinicians examining their first case of donovanosis think it is carcinoma, regardless of whether the lesion is of the vulva or the cervix. Adequate biopsies must be taken and carefully studied. Pathologists can also be misled. The hyperplasia and dysplasia of squamous epithelium at the edge of an ulcer can easily be mistaken for low-grade squamous cell carcinoma. Occasionally, however, the diagnosis is carcinoma.

The clinical diagnosis is suggested by the clinical appearance of the lesion or lesions. A diagnosis can be made from a stained crush preparation from the lesion. A piece of clear granulation tissue from a lesion is spread against the slide which is then air-dried and stained with Wright or Giemsa stain.

The diagnosis of granuloma inguinale is almost invariably based on the identification of classic Donovan bodies in biopsy material. Donovan bodies appear as clusters of blue or black staining with an organism's 'safety pin' appearance (from bipolar chromatin) in the cytoplasm of large mononuclear cells. Biopsies should be taken radially through the edge of the ulcer and include some of its base. The affinity of the intracysts of *C. granulomatis* for silver salts facilitates the recognition of the Donovan bodies. Because Donovan bodies are very hard to find, they may be more readily demonstrated in tissue spreads stained with Giemsa's stain than in histologic sections stained with either hematoxylin and eosin or silver stains. In either case, success in their identification depends on the sharp eyes and persistence of the pathologist, who often has to search many slides in order to establish the diagnosis of donovanosis.

Therapy

Calymmatobacterium granulomatis is susceptible to a wide number of antibiotic preparations that interfere with protein synthesis. The tetracyclines (0.5 g every 6 hours orally) are the drug of choice. Trimethoprim-sulfamethoxazole (two tablets every 12 hours) has been effective. Chloramphenicol (0.5 g every 8 hours orally) is reserved for resistant cases. While Freinkel and Counihan have found both ampicillin and erythromycin to be somewhat erratic in efficiency, the combination of ampicillin and erythromycin has been found to be satisfactory in the treatment of pregnant patients. Treatment should be continued until the lesions have healed completely, which usually takes three weeks. Long-standing lesions may be so mutilating that adjunctive surgical care may be necessary. The elimination of secondary infection by topical cleansing and antimicrobial therapy accelerates healing. Relapses are frequent; some cases require prolonged courses of antibiotic therapy. It is wise to treat infection vigorously and to insist on compulsive follow-up even after apparent cure.

The local areas of 'elephantiasis' remaining after effective treatment of active infection are often uncomfortable and cause cosmetic embarrassment. Once infection is cured, local excision of such focal swelling can be carried out.

CHANCROID *(HAEMOPHILUS DUCREYI)*

Chancroid is a superficial infection of the external genital tract caused by *Haemophilus ducreyi*. *Haemophilus ducreyi* has a worldwide distribution but is found more frequently in tropical and subtropical countries. Within the United States, disease is more prevalent in the southern states.

Table A II.3 Clinical characteristics of chancroid ulcer

Number	usually multiple but may occur as an isolated lesion
Shape	irregular
Depth	deep
Purulence	present
Tenderness	present
Induration	none

The infection is disseminated venereally. Genital lesions appear three to 14 days after sexual contact and may be single or multiple. The initial lesion is usually one or more small erythematous macules which rapidly become vesicular pustules. The lesion ruptures, leaving behind a small circumscribed ulcer with an erythematous base (Table A II.3). The ulcer is painful and tender to palpation and is characterized by a non-indurated base, painful overhanging edges, and ragged margins. The lesion frequently has an erythematous halo. The base of the ulcer is covered with a dirty looking, necrotic, grayish exudate. Lymphadenitis occurs in approximately 30% of the cases. The lymphadenopathy is regional and is often unilateral (generally on the same side as the lesion). Without adequate therapy there may be extension of the process from the lymph nodes to the overlying skin, resulting in draining sinuses.

Superinfection of the ulcer or ulcers, especially by fusospirochetes, may lead to extensive destruction of the external genitalia (phagedenic chancroid).

Diagnosis

Diagnosis is inferred by the demonstration of small Gram-negative rods often with bipolar staining.

The bacteria are often seen in short chains or parallel arrays (‘school-of-fish’ or ‘fingerprint’ patterns). They may be cultivated with difficulty. A presumptive diagnosis can be inferred from the identification of short Gram-negative rods in strands on smears stained with Gram or Wright stain, and an ulcer characterized by non-induration of the base and painful, ragged, overhanging margins. Specific fluorescent antibody staining of bacteria in smears from suspected lesions provides a means for substantiation of the diagnosis; unfortunately, the availability of this diagnostic procedure is limited. Biopsy of the lesion is useful since it eliminates granuloma inguinale, syphilitic chancre, and herpetic ulcer from diagnostic consideration.

A definitive diagnosis established with isolation of the organism in Gonococcal agar supplemented with bovine hemoglobin and fetal calf serum or Mueller-Hinton agar supplemented with chocolatized horse blood is required to maximize recovery on primary isolation.

Therapy

The emergence of *Haemophilus ducreyi* that is multiply resistant to antibiotics has limited the effectiveness of many antimicrobials for therapy of chancroid. Trimethoprim-sulfamethoxazole (160/800 mg twice a day for seven days) or erythromycin (500 mg four times a day for seven days) have been the drugs of choice.

Current therapeutic regimens include:

Erythromycin: 500 mg four times a day until the ulcers and/or adenopathy have resolved

Ceftriaxone: 250 mg intramuscularly once

Trimethoprim-sulfamethoxazole: 800 mg/1600 mg orally twice a day for seven days

Ciprofloxacin: 500 mg twice daily for three days

Erythromycin-resistant strains of *H. ducreyi* have been reported from Singapore. Erythromycin is highly effective in treating chancroid in dosages of 500 mg four times a day for at least seven days. Because this dosage of erythromycin can cause gastrointestinal discomfort, physicians should be alerted to poor patient compliance. Shorter courses may be effective, but such data are lacking.

Ceftriaxone appears to be as effective as erythromycin and has the advantage of being administered as a single intramuscular dose of 250 mg. The drug is extremely active against *H. ducreyi* in vitro and no strains resistant to it, or to cefotaxime, have been reported.

The efficacy of trimethoprim-sulfamethoxazole appears to be less than that of erythromycin or ceftriaxone, particularly in areas where trimethoprim resistance is common. Ciprofloxacin (500 mg twice daily for three days) is highly effective. A bolus dose of 750–1000 mg can achieve almost comparable results.

With effective therapy, a clinical response, first subjective and then objective, should be apparent within several days of instituting therapy. A subjective response (diminished tenderness and pain) occurs within 48 hours of institution of antimicrobials. An objective response generally occurs within 72 hours and almost always within seven days. Healing takes 10 to 11 days after institution of therapy. Large ulcers may require relatively longer time periods to heal. Patients should be seen seven days after beginning therapy, when objective signs of ulcer healing will be present in virtually all successfully treated patients, and adenopathy should be less painful and usually smaller. Some nodes may progress to fluctuation despite adequate therapy and require needle aspiration through normal skin to prevent spontaneous drainage.

While ulcers in successfully treated patients respond to therapy quickly, adenopathy may not, and progression to fluctuation is not necessarily a sign of treatment failure.

If by day seven a clinical response has occurred and therapy has been taken as directed, therapy need not be continued. If a clinical response is not apparent, the clinician should reconsider the clinical diagnosis of chancroid or, if it has been confirmed by a culture, consider a mixed infection, e.g. herpes and chancroid.

Sexual contacts of patients with chancroid should be examined and treated with an effective antimicrobial regimen, whether lesions are present or not. Asymptomatic carriage of *H. ducreyi* appears to be uncommon, but colonization of the vagina, penis, and mouth in the absence of lesions has been described. Initial treatment guidelines recommended that therapy be continued for at least ten days and until clinical resolution of ulcer(s) and adenopathy. Subsequent studies have shown high efficacy of one- to seven-day courses of therapy and indicate that antimicrobial courses of ten days offer no therapeutic advantage over shorter courses, even though ulcers have not completely healed and adenopathy is persistent.

Inguinal adenopathy will occur in 30% of patients with chancroid. Because of the possibility of concomitant syphilitic infection, darkfield analysis of all lesions should be performed. Serologic tests for syphilis should be obtained during therapy. If the antimicrobial agent utilized will not eradicate incubating syphilis, the serological test should be repeated 6–8 weeks after its termination.

HERPETIC GENITAL ULCERS (HERPES SIMPLEX VIRUSES)

Initial contact with herpes simplex viruses usually occurs early in childhood and involves herpes simplex virus type-1 (HSV-1). About 10% of primary infections with HSV-1 are clinically overt.

HSV-1 is the causative agent for most non-genital herpetic lesions: herpes labialis, gingivostomatitis, and keratoconjunctivitis. Infection of the female genital tract by HSV-1 may occur at this time; however, the virus can often be simultaneously cultured from non-genital sites, suggesting that genital involvement is most often a secondary phenomenon.

Herpetic vulvovaginitis due to HSV-1 is observed primarily at the time of initial herpetic infection in infancy or early adolescence; subsequently, type 2 becomes increasingly more prevalent. Type 2 antibodies usually appear first about the time of puberty and exhibit a significant increase during the prime reproductive years. The greatest incidence of overt type 2 infection occurs in women in their late teens and early twenties.

HSV-2 is recovered predominantly from the female genital tract. Epidemiologic data strongly support the thesis that dissemination of the type 2 strain is primarily but not exclusively contingent on venereal transmission. The incidence of specific antibody approaches 100% among prostitutes. Following exposure to males with active herpetic lesions of the genitalia, 50–90% of susceptible sexual partners develop infection.

HERPETIC VULVOVAGINITIS

Primary infection

Primary genital infection due to HSV-2 may be asymptomatic or may be associated with severe symptoms. In primary vulvovaginitis the genital lesions on the vulva, vagina, cervix, occur between 2 and 7 days following exposure to infectious virus. Like those in

primary herpes labialis, the lesions are multiple and larger than those observed in recurrent disease or in those who have had prior infection with HSV-1. At this time, patients usually experience vaginal discharge, discomfort, and pain. The mucocutaneous lesions are prone to trauma. The initial vesicles rupture and tend to become secondarily infected. They subsequently appear as shallow, eroded, painful ulcers covered by a shaggy white membrane. Regional lymphadenopathy is readily demonstrated as the consequence of virus replication in the sites of lymphatic drainage as well as nodal stimulation by secondary bacterial infection.

Whereas local symptoms of dysuria, soreness of the vulva and vagina, dyspareunia, and a sudden increase of discharge are common in both primary and recurrent infection, systemic symptoms (malaise, myalgia, and fever) are virtually restricted to primary herpetic infection (Table A II.4). These symptoms reflect the viremia engendered during primary infection. Whether a systemic response to infection occurs is dependent upon the presence or absence of heterologous antibodies to HSV-1.

The lesions tend to persist for 7–10 days. However, when secondary bacterial, mycotic, or protozoan infection is not treated, the lesions may persist for 2–4 weeks.

Primary herpetic infection may occur on the cervix. The appearance of extensive cervical involvement may mimic that observed with squamous cell carcinoma of the cervix.

Recurrent infection

Confinement of the ulcers to one area of the vulva, vagina, or cervix is more common in recurrent forms of the disease. The ulcers tend to be limited in size and number. Cervical involvement may occur as a diffuse cervicitis or as a single large ulcer. Local symptoms predominate over systemic symptoms, with increased vaginal discharge or pain being the usual presenting complaint.

In certain women it can be demonstrated that once it is involved, the genital tract is the site of intermittent virus replication. Virus shedding, particularly from the cervix, may be demonstrated intermittently for 2 weeks. The titer of virus is significantly reduced compared to

Table A II.4 Clinical differences between primary and recurrent vulvovaginitis due to herpes simples virus type 2

Signs or symptoms	***Primary***	***Recurrent***
Number of lesions	Multiple	Scattered 1 to 3
Location of lesions	Tend to involve both labia and vagina; cervix may be concomitantly involved	Limited involvement of vulva, vagina or cervix
Size of lesions	Variable; tend to be larger than those observed in recurrent disease	Tend to be smaller
Inguinal adenopathy	Present	Usually absent
Viremia	Occurs	Absent

Systemic symptoms (malaise, myalgia, fever)	Present*	Absent
Local symptoms (dysuria, itching, dyspareunia)	Present	Present
Specific antibody titer	Greater than fourfold rise observed between pre- and postconvalescent sera	Usually no significant change

*Only in the absence of preexisting antibodies to herpes simplex type 1

the level of recoverable virus when clinically overt lesions are present.

Random sampling of a female population by cytologic examination of routine cervical smears reveals a 0.3–5% incidence of herpes infection, depending upon the patient population studied. The higher figure is derived from patients attending venereal disease clinics. If careful virologic screening is superimposed, an additional 1–2% may be identified. The total figure is roughly comparable to the incidence of recovery of HSV-1 from the oropharnyx in a random sample study.

Diagnosis

Infection may be documented in several ways. Being DNA viruses, the HSV produce histologic stigmata indicative of virus replication. Papanicolaou smears of a given lesion may demonstrate large multinucleated cells containing eosinophilic intranuclear inclusion bodies. Cytological tests have a maximum sensitivity of 60–70% when dealing with overt clinical disease. Both the Papanicolaou and Zanck smears are poor screening procedures. The presence of multinucleated giant cells is predominantly a phenomenon of herpetic involvement at free surfaces, as opposed to the single intranuclear inclusion body observed within organ tissues. Biopsy in conjunction with cytologic analysis of a cell preparation from the lesion very often leads to a diagnosis, even in the absence of virus isolation studies.

The recent introduction of enzyme-linked immunoabsorbent assays and DNA probes gives clinicians additional diagnostic tools. In culturing for HSV, overt lesions that are not in the ulcerated state should be unroofed and the fluid sampled. In the absence of an obvious lesion, the following procedure should be used. Sample the endocervix and break off the swab into the vial. Take a second swab and sample the posterior vaginal pool and then the lower third of the vagina. Break off the swab into the same vial (otherwise the patient will be charged for two cultures). Be sure the culture is kept on ice and taken directly to the virology laboratory. Be sure to schedule all patients for morning clinics. When cultures get to the laboratory, they should not be frozen before inoculation into tissue culture. Freezing, even at −60ºC, will reduce the titer of the specimen by one to two logs of virus. While this magnitude of loss may not be critical when dealing with overt lesions, it will make a significant difference in blind screening of the endocervix/vagina. Because of the significant loss of activity of the virus when frozen, it is best that suspected specimens are not frozen prior to inoculation into an appropriate virus isolation system. Virus isolation can be readily achieved in many primary or continuous human tissue culture cell lines or on the chorioallantoic membrane of embryonated eggs.

Serologic testing is of relatively limited value because of the frequent presence of cross-reacting antibodies to the heterologous virus. Only if the acute-phase serum had a non-detectable or very low titer and the convalescent serum obtained 10–14 days after the onset of clinical disease demonstrated a fourfold or greater rise in the complement titer or the presence of IgM specific antibodies could one serologically distinguish between primary and recurrent infections. The presence of an antibody titer in the initial specimen obtained at the onset of disease, and the failure of the titer to exhibit a fourfold or greater rise in the convalescent specimen or the presence of IgM specific antibodies argues strongly for recurrent infection with HSV-2 or prior infection with HSV-1. The distinction between primary and recurrent infection (Table A II.4) is of more than just academic interest when a gravida is concerned. Primary infection with either virus, in the absence of cross-protecting antibodies, exposes the fetus to the small risk of transplacental infection.

Management

Currently, most non-drug therapeutic measures are directed toward providing the patient with symptomatic relief from pain and vaginal discomfort. Almost invariably, the ulcers are secondarily infected by either bacterial or mycotic organisms, or both. If one aggressively treats the superinfection, the patient will be markedly improved within 24 hours and relatively symptom-free in 72 hours.

The inflammatory process renders the perineum exquisitely tender in primary herpetic vulvovaginitis. Therapy requires the ability to do a pelvic examination. Not infrequently, parenteral analgesia is required. The therapeutic regimen at Creighton University is as follows: The perineum is cleansed with a 4×4 sterile gauze pad or with cotton drumsticks. A wet mount and KOH preparation are obtained and the major lesions are then selected for documenting the herpetic etiology. If the lesions are still in the vesiculopustular stage of the disease, they are unroofed. Scrapings of the base and margins of either the unroofed vesicles or ulcerated lesions are obtained with a wooden spatula and smeared onto a clean slide for cytologic analysis. The diagnosis of herpes is made by the finding of the characteristic giant cells with intranuclear inclusion bodies. Where facilities exist, cultures for herpes simplex virus should be obtained.

At this point, one can introduce a speculum to see if there are intravaginal or cervical lesions. A patient with one sexually transmitted disease is in a high-risk category for another. It is imperative that a culture be taken at this time for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and that serology be done for *Treponema pallidum*, prior to the institution of systemic therapy.

The vaginal canal is dried with sterile drumsticks, and an intravaginal medication (determined by results of the KOH preparation and wet mounts) is instilled. If neither *Trichomonas vaginalis* nor *Candida albicans* is identified, 2% clindamycin intravaginal cream or povidone iodine is applied intravaginally; otherwise, intravaginal medications should be specific for the major superinfecting organism. To avert the problems of local maceration, one should use either Sultran® in a zinc oxide base or simple white petroleum jelly as a lubricant. With this aggressive regimen, the lesions tend to clear in 2–5 days.

Failure to eradicate secondary mycotic or pyogenic infection results in prolongation of the inflammatory vulvar edema and retardation of healing. The edema associated with the ulcerative stage of the disease is an important contribution to the patient's overall pain and discomfort. Local analgesic ointments are effective not only in eliminating the pain associated with the vesicularulcerative stage of infection, but also, if dispensed in an appropriate ointment base, in protecting the skin from further maceration and bacterial overgrowth.

Topical or systemic administration of steroids has no place in the treatment of herpetic vulvovaginitis. Corticosteroids, by their ability to stabilize lysosome membranes and inhibit the production of interferon, exert a deleterious effect in experimental viral and mycotic infections. Although the exact mechanism for the immune elimination of viruses from a host is not yet completely defined, current data confer the central role to interferon. Although effective in combating the associated inflammatory edema, the corticosteroids enhance virus replication.

Antiviral therapy

Zovir

Zovir (acyclovir) is the prototype antiviral drug for human use in the treatment of acute herpetic infection. Efficacy depends on the way the drug is administered. Topical acyclovir (5% ointment) is effective only in selected clinical situations. Oral acyclovir can be highly effective in aborting recurrent episodes of genital herpes.

Mechanism of action Acyclovir itself is not active against the herpes virus. It is selectively converted to another form in the body, triphosphate, by herpes virusinfected cells. This conversion does not occur to any significant degree in normal cells. Acyclovir triphosphate interferes with herpes simplex viral enzymes and in so doing inhibits viral replication.

Topical acyclovir

Topical acyclovir is currently available only as a 5% ointment which is supplied in 15 g tubes. It is recommended that a sufficient quantity should be applied to adequately cover all lesions every 3 hours, 6 times per day, for 7 days. A finger cot or rubber glove should be worn when applying the drug to prevent autoinoculation of other body sites and transmission of infection to other persons.

Timing of therapy To be effective, drug application should be initiated as early as possible following the onset of signs and symptoms.

Impact of infectivity Acyclovir will diminish the amount of virus present and its duration of shedding; hence, theoretically, it should alter infectivity.

Valtrex

Valtrex (valacyclovir) is the L-valyl ester of acyclovir. The formulation allows for greater drug absorption. Once absorbed, valacycloviir is almost completely converted to acyclovir after oral administration. The higher oral bioavailability of valacyclovir results

in greater or comparable drug concentration which can be achieved by taking the medicine less frequently. To date, the clinical results and safety profile achieved with valacyclovir and acyclovir in acute outbreaks are comparable. The recommended dosage is 500 mg twice a day for five days.

Famvir

Famvir (famciclovir), an oral prodrug of the antiviral agent penciclovir, has been recently introduced. Like valacyclovir, famciclovir is selectively absorbed and rapidly converted into its active ingredient. It has a long intracellular half-life. The recommended dosage is 125 mg bid for five days. Initial therapy should be within the first 3–5 hours from the onset of sign or symptom. Neither valacylovir nor famciclovir have been adequately studied as to their ability to suppress recurrent episodes.

The therapeutic efficacy of topical acyclovir and oral acyclovir in the treatment of active infections has been disappointing. The recommended regimen for first episode of disease in an immunocompetent host is acyclovir 200 mg p.o. five times per day for 10 days. The drug is a purine analog which is a substrate for the viral enzyme thymidine kinase; this converts the compound to acyclovir triphosphate which then inhibits viral DNA synthesis. Acyclovir reduces the virus titer present and shortens duration of disease against placebo but is not superior to aggressive local therapy. To have efficacy, the drug must be administered at the time of prodromal symptomatology, i.e. cutaneus tingling, etc. There is a subgroup of patients with frequent recurrent disease who appear to benefit from prophylactic longer term use of the medication. Because the long-term risks are not fully assessed, prophylactic therapy with the drug should be limited to less than six months. The current treatment schedule for suppression of recurrent genital herpetic infection is acyclovir 200–400 mg p.o. two times daily for up to six months. This regimen is advocated for women with more than six symptomatic recurrences per year.

CHLAMYDIA TRACHOMATIS LYMPHOGRANULOMA VENEREUM (L) STRAINS

Although its distribution is worldwide, Iymphogranuloma venereum is more common in tropical and semitropical climates. The mode of transmission is believed to be through coitus or intimate physical contact. A number of small endemic foci have been traced to a specific prostitute. The disease may also be disseminated by close non-sexual contact as well as by autoinoculation. Disease has occurred in laboratory workers. Although a grippe-like syndrome characterized by fever, malaise, headache, and anorexia may occur, it is rarely the chief presenting complaint in patients with lymphogranuloma venereum. Fever is present in over 50% of the cases and tends to correlate primarily with the severity of illness. When lymphogranuloma venereum involves the vulva it is as part of its inguinal syndrome.

Genital lesions

The initial genital lesion which develops varies from a slight erosion to a small cutaneous herpetiform lesion. It may either disappear or develop into an ulcer. The lesion is painless and only slightly tender to palpation. It exhibits ill-defined shallow margins and a fibrogranular base. The fourchette, urethral meatus, and medial surface of the labia are the usual sites of primary lesions. Clinical recognition of infection at this stage is the exception, not the rule. When multiple lesions are present, the adjacent labia or clitoris are often edematous. In the absence of secondary infection, most of the lesions will have healed prior to the onset of lymph node enlargement.

More than 50% of infected patients manifest no clinical symptoms. While most male patients develop inguinal adenopathy during the course of disease, this manifestation is relatively unusual in females. The adenopathy may vary from shoddy nodes to fluctuant masses often associated with draining sinuses. Lymph node involvement is indicative of lymphatic drainage from the primary lesions, and consequently unilateral adenopathy is not uncommon. The regional glands draining the primary site of infection, particularly in the male, enlarge dramatically and may appear as a series of buboes. Sixty per cent of the buboes rupture, discharging a copious watery to purulent granular exudate.

The early histologic appearance of lymph nodes is that of diffuse reticular and lymphocytic hyperplasia. In the more advanced lesion, macrophages appear in significant numbers prior to the development of central necrosis. The macrophages assume a palisade-like arrangement around the central focus of necrotic cellular debris. Plasmacytosis is one of the important supplementary criteria in the histologic diagnosis of lymphogranuloma venereum. Healing is associated with fibroblastic proliferation and (ultimately) with the replacement of the diseased foci by fibrous connective tissue. Extensive cutaneous scarring may suggest the diagnosis in a patient seen for the first time late in the course of the disease.

If urethral involvement occurs, it exhibits the same sequential pattern—first ulceration and then destructive lesions with healing by fibrosis. Patients with partial urethral destruction may remain continent as long as the distal portion of the urethra is intact. Partial obstruction may cause difficulty in voiding. The resultant symptoms are those of urethral obstruction. Complete urethral destruction represents a difficult therapeutic challenge, necessitating surgical reconstruction.

Diagnosis

The disease is difficult to diagnose since the female patient is more likely to present with the genitorectal than with the inguinal syndrome or with inguinal adenopathy in a subclinical form. With primary infection she may complain of a small boil on the vagina or a slight discharge or irritation. Most often the small shallow red ulcers with flat margins due to lymphogranuloma venereum escape clinical detection. The second stage of disease, in which adenitis predominates, may pass unnoticed until a late phase in which fibrosis or tissue destruction has developed. The patient may complain of discomfort. Lymphogranuloma venereum must be considered in the differential diagnosis of any fistulous tract involving the perineum or inguinal adenopathy (Table A II.5).

Table A II.5 Differential diagnosis of inguinal adenopathy associated with a presumed venereal disease

Disease	*Genital lesion*	*Nodal involvement*	*Cutaneous lesions*
Granuloma inguinale	Extensive in males; less evident in females	Involvement of lymph nodes; draining cutaneous sinuses; late in the course of the disease; nodes become tender	Primary skin infection with superficial ulceration
Lymphogranuloma venereum	Occurs but is extremely transient in nature	Bilateral node involvement is determined by site of primary lesion	Multiple sinus tracts draining a thick, creamy exudate
Chancroid	Usually present	Primarily unilateral with limited involvement of lymph nodes	Acute, with crater-like slough
Genital tuberculosis	None	Bilateral inguinal adenopathy	Pleomorphic, often with sinus tract draining scanty but thick exudate
Syphilis	Usually present	Bilateral; firm, rubbery nodes	Protean in its clinical manifestations

Laboratory results, with the exception of complement fixation or micro-immunofluorescent tests for Iymphogranuloma venereum, are inconclusive. Abnormalities in the white blood cell count include mild to marked leukocytosis with a relative lymphocytosis. Biologically false-positive serologic tests for syphilis not infrequently occur. In longstanding disease, the albumin-globulin ratio is inverted.

Serologic confirmation of prior and/or concurrent antigenic experience with *Chlamydia* organisms coupled with a characteristic disease clustering makes the diagnosis of lymphogranuloma venereum. Aspiration of fluctuant nodes can be implemented as a therapeutic adjunct in adenitis. Aspiration of suppurative nodes in lieu of spontaneous rupture has been advocated and appears to be free of significant complications. Aspiration is best achieved with a number 20 needle, inserting it through adjacent non-involved skin rather than aspirating the lesion directly through skin overlying the node. A patient with significant disease must be monitored for possible development of vulvar carcinoma. Biopsy of any suspicious lesion is mandatory

TREPONEMA PALLIDUM (SYPHILIS)

A vulvoulcerative disease due to *Treponema pallidum* is the consequence of primary syphilis. The time required for development of the primary lesion is partly a function of the number of organisms establishing the initial infection and their subsequent replication at the portal of entry. Infections with a large inoculum (e.g. 10^7 organisms) may cause a chancre in 5 to 7 days. The inoculation of 50 to 100 organisms is followed by an

incubation period of about three weeks. The longest incubation period appears to be approximately five weeks.

The primary lesion consists of a small papule which breaks down to form a superficial, painless ulcer with a clean granular base and firm scrolled margins. Classical chancres are solitary lesions. However, multiple chancres have been identified in up to 40% of individuals with primary syphilis. Histologic analysis reveals, in the absence of secondary infection, an extensive plasma cell and lymphocytic infiltration. Characteristic of the lesion is the effect of *T. pallidum* on the small blood vessels. Extensive endothelial proliferation in association with a significant plasma cell infiltrate should suggest a diagnosis of primary syphilis on histologic grounds alone.

When dissemination from the portal of infection to the regional lymph nodes occurs during the primary phase of the disease, the result is 'satellite' buboes (Table A II.5). Regional adenopathy normally accompanies the chancre of primary syphilis. The adenopathy usually develops a week after the appearance of the initial lesions. Untreated, a chancre will persist for two to eight weeks and then spontaneously disappear.

Table A II.6 Preliminary 1997 therapeutic recommendations of the Centers for Disease Control

PRIMARY AND SECONDARY SYPHILIS

Recommended regimen for non-pregnant women

Non-allergic patients with primary or secondary syphilis should be treated with the following regimen*:

Benzathine penicillin G, 2.4 million units IM in a single dose

Penicillin allergy

Non-pregnant penicillin-allergic women who have primary or secondary syphilis should be treated with the following regimen:

Doxycycline 100 mg orally 2 times a day for 2 weeks

or

Tetracycline 500 mg orally 4 times a day for 2 weeks

RECOMMENDED REGIMEN FOR PREGNANT WOMEN

Treatment during pregnancy should be the penicillin regimen appropriate for the woman's stage of syphilis.*

Penicillin allergy

There are no proven alternatives to penicillin. A pregnant woman with a history of penicillin allergy or positive skin test should be treated with penicillin after desensitization.

Tetracycline and doxycycline are both FDA Pregnancy Category D and usually not used during pregnancy. Erythromycin (FDA Category B) should not be used, because it does not reliably cure an infected fetus.

*Parenteral penicillin G is effective in achieving local cure (healing of lesions and prevention of

sexual transmission) and in preventing late sequelae. However, no adequately conducted comparative trials have been performed to guide the selection of an optimal penicillin regimen (i.e., dose, duration, and preparation). Penicillin regimens should be used to treat all stages of syphilis among HIV-infected patients. Some experts recommend additional therapy in some settings. A second dose of benzathine penicillin 2.4 million units IM may be given 1 week after the initial dose for women with primary, secondary, or early latent syphilis. Ultrasongraphic signs of fetal syphilis (i.e., hepatomegaly and hydrops) indicate a higher risk for fetal treatment failure.

Physical examination reveals enlarged, firm but tender lymph nodes, reflecting both organismal replication and reticular and lymphocytic cellular proliferation.

Irrespective of the subsequent clinical course, the chancre heals spontaneously. In approximately 30% of cases disease is limited to replication at the portal of entry, and even without therapy, eradication of the infection may occur in conjunction with the disappearance of serologic evidence of syphilitic infection as measured by non-treponemal tests.

From regional lymph node drainage of the portal of infection, hematogenous dissemination characteristic of the secondary phase of the disease occurs.

Diagnosis

Confirmation of a syphilitic chancre depends on the demonstration of *T. pallidum* on darkfield microscopic examination. The lesion should be cleansed and abraded with gauze to induce superficial bleeding, and the blood blotted away. Once the serum begins to ooze, a small aliquot is then placed on a glass slide and a cover slide applied. Darkfield analysis should be completed before the slide dries. If a specimen must be transported a short distance, the serum specimen should be collected in a relatively large-bore capillary tube and one end temporarily sealed with clay.

An alternate means of diagnosis confirmation entails the use of biopsy taken from the rim of the lesion. Spirochetes are not detectable by conventional staining techniques. Demonstration of the organism requires utilization of the ability of silver salts to delineate the organisms' contours.

By the time the primary lesion is detected, both humoral and cell-mediated immune mechanisms have been activated.

The serologic tests for the detection of *T. pallidum* can be broken down into two broad categories: nontreponemal (flocculation and complement-fixation tests) and treponemal (*T. pallidum* immobilization [TPI], *T. pallidum* microhemagglutination [TPHA], and fluorescent treponemal antibody [FTA] tests). The former are serologic assays for antibodies that react with cardiolipin, a non-specific antigen; the latter, by using *T. pallidum* or an avirulent strain of *T. pallidum*-known as the Reiter treponeme—as the test antigen, detect specific antibodies.

Therapy

The therapeutic recommendations of the CDC are listed in Table A II.6.

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APPENDIX III

Understanding abdominal pain of gastrointestinal etiology

As obstetricians and gynecologists move into the area of primary care, they need to understand the significance of abdominal pain beyond that associated with acute salpingitis, pyelonephritis, ectopic pregnancy, and torsion of adrenal masses. This segment deals with the principal pain patterns encountered in the common care of women, and in doing so, assists physicians to identify when abdominal pain is of infectious etiology.

William Olser once said, let me take the history and let anyone do the physical examination and I will give you the correct diagnosis in 80% of the cases'. One of the problems with our technology is our growing dependence on it. Too often, we abort a detailed history because of the ability of X-rays or fiberoptic technology to establish a probable or definitive diagnosis. While a good history can only imply what the probable etiology is, it will tell you exactly where that technology needs to be applied. The principal laboratory modalities which are valuable in the analysis of acute abdomen are white blood cell count, its differential count, and an erythrocyte sedimentation rate. A problem associated in dealing with the gastrointestinal tract is the difficulty differentiating between the pain associated with organic disease and that caused by functional disturbances.

Perception or description of a pain's character arising from the same lesion in the gastrointestinal tract will vary depending upon the type of person involved (e.g. two patients with comparable duodenal ulcers may complain of agonizing pain or of a slight gnawing sensation). Differences in intensity at different points in time may similarly alter perception of the character of pain. The threshold for pain varies at different times in the same person. One day a patient may complain of burning epigastric pain, whereas on another day the sensation arising from the same source may be described as a vague discomfort. While there is potential variation in the character of sensation, localization of pain caused by a disturbance in a given part of the gastrointestinal tract tends to be referred to a specific site on the abdomen (indirect visceral pain/somatic referral).

This type of pain is distinct from direct splenic visceral pain. Somatic pain is usually a deep, heavy pain felt in the region of the diseased organ. With somatic pain, the area of cutaneous referral is often accompanied by cutaneous hypersensitivity within the same segment of distribution.

The principal tool in diagnosing acute abdominal pain emanating from one of the five cardinal organ systems:

(1) gastrointestinal tract;
(2) urinary tract;

(3) female genital tract;
(4) biliary tract; and
(5) blood vessels

are:

(a) character of pain;
(b) pain localization;
(c) pain radiation; and
(d) factors which ameliorate or exacerbate the pain.

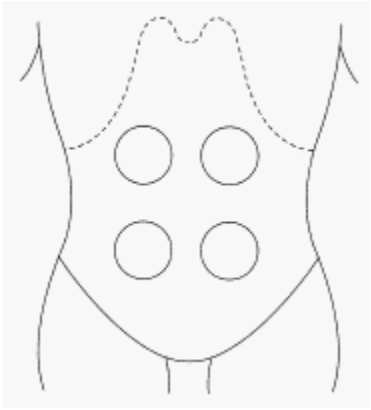

Figure A III.1 Infectious diseases eliciting abdominal pain involving one or more quadrants. Four-quadrant pain. Potential etiologies:

(1) Ruptured tubo-ovarian abscess (TOA) into the peritoneum

(2) Perforated viscus, especially peptic ulcer

(3) Peritonitis due to other causes

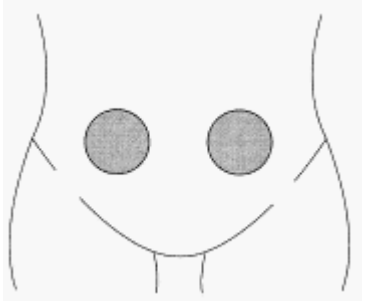

Figure A III.2 Bilateral lower quadrant pain. Potential etiologies:

(1) Acute appendicitis

(2) Acute salpingitis

(3) Ruptured TOA

(4) Infected ruptured ectopic pregnancy

This segment focuses on the two former aspects of abdominal pain.

CHARACTER OF PAIN

Character of the pain can assist the physician in focussing on the probable diagnosis. Crampy or gripping, intermittent pain (colic) is indicative of a smooth muscle site of disease.

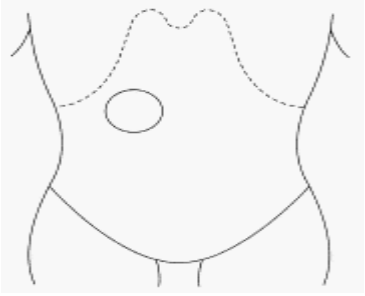

Figure A III.3 Tenderness and rigidity in the right hypogastrium. Potential etiologies:

(1) Leaking duodenal ulcer

(2) Acute cholecystitis

(3) Appendicitis (high appendix)

(4) Right basilar segment pleurisy

PAIN LOCALIZATION

Potential diagnostic significance of localized abdominal pain

Initial localization of pain begins using the simple four quadrant localization. A superior system places pain in the context of right and left hypogastric, periumbilical and right and left iliac areas and then focuses on midline (central) pain.

PAIN EMANATING FROM THE GASTROINTESTINAL TRACT

Pain involving the substernal region, the upper portions of the sternum, tends to be primarily esophageal etiology. Lesions involving the upper one-third of the esophagus are usually referred to the episternal notch and the first portion of the manubrium. On rare occasions, this pain sometimes is referred to the back of the throat.

Esophageal pain is always in the midline under the sternum. Lesions in the midesophageal area are referred to the middle portion of the sternum corresponding to C3–C4 distribution. Disease in the inferior portion, the cardiac portion of the esophagus, will be referred to the infrasternal notch.

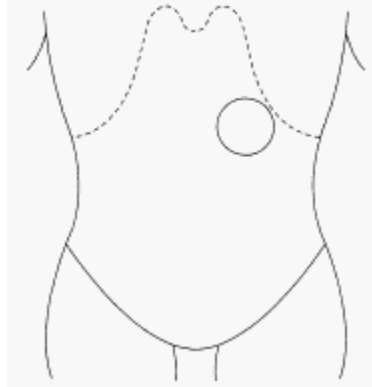

Figure A III.4 Tenderness and rigidity in the left hypogastrium. Potential etiologies:

(1) Perforated gastric ulcer (subphrenic abscess)

(2) Jejunal diverticulitis

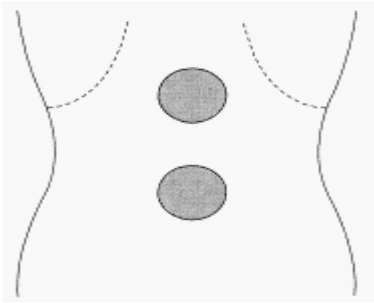

Figure A III.5 Tenderness and rigidity in the periumbilical area. Potential etiologies:

(1) Earliest stage of acute appendicitis

(2) Small bowel obstruction

(3) Acute pancreatitis

(4) Acute gastritis

(5) Coronary occlusion

Stomach

Prior abdominal diseases, particularly those which result in operative procedures, may modify pain in such a way that it is no longer referred to the usual site. Pain from these two sites are referred to the epigastrium. With involvement of cardiac portions of the stomach, pain is referred to the epigastrium near the xyphoid while that from the pyloric end of the stomach is felt lower in the epigastrium. Pain may be referred through to the back or to the left side in the T6-T7 distribution.

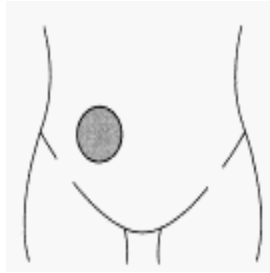

Figure A III.6 Tenderness and rigidity in the right iliac region. Potential etiologies.

(1) Below the epigastrium is obstruction of the transverse colon

(2) Appendicitis, late stage

(3) Ileocecal colitis

(4) Meckel's diverticulum

(5) Acute cholecystis (low gallbladder)

(6) Biliary peritonitis

(7) Ruptured TOA

(8) Right annexal torsion

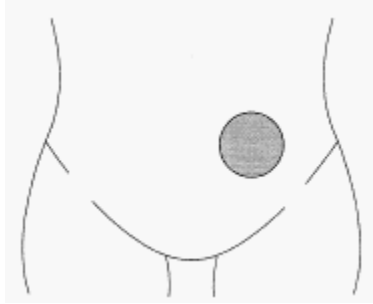

Figure A III.7 Tenderness and rigidity in the left iliac region. Potential etiologies:

(1) Diverticulitis

(2) Ruptured TOA

(3) Left annexal torsion

(4) Obstruction of transverse colon

Duodenum

Duodenal pain is referred to the midline and mid-epigastrium. When referred to the back, localization tends to be under the scapula or the right of the midclavicular line at the level of the seventh rib. Lesions in the second portion of the duodenum may result in pain referred straight through to the back or around the right costal margin to the back at the same level as the pain is noted anteriorly

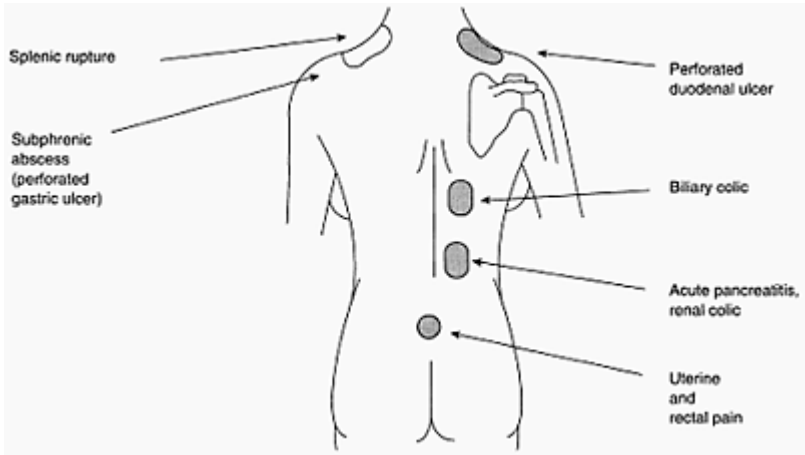

Figure A III.8 Patterns of referred back pain in acute abdominal situations

Table A III.1 Importance of referral back pain

Posterior back pain in the region of the tenth dorsal vertebra is seen with duodenal peptic ulcer disease and posterior penetration
Gallbladder occlusive disease
Cancer of the rectum
Disease of the hepatic flexture
Disease of the body and tail of the pancreas

Jejunal ileum

Pain from the jejunal/ileum tends to locate near the midline in the region of the umbilicus. Referred pain from the large bowel is primarily below the umbilicus, halfway between the umbilicus and the pubic symphysis.

Cecum

Disease located in the cecum, just below the ileocecal valve, will produce pain at McBurney's point. Disease involving the hepatic or splenic flexure results in a more lateral displacement to the midclavicular line. Fixation of the flexures is thought to be responsible for this modification of referred pain.

Colon

When disease is located in the descending colon, the pain tends to occur more on the left side between the umbilicus and toward the left lower quadrant. There is a closer correlation between somatic pain and its splenic cutaneous referral. When disease involves the rectosigmoid or rectum, the pain is again in the midline just above the pubis. Disease of the terminal ileum and ascending colon may radiate from the periumbilical area laterally; however, maximum symptomatology will be midline.

SIGNIFICANCE OF POSTERIOR RADIATION OF ABDOMINAL PAIN

Back pain is not common with diseases of the gastrointestinal tract and female genital tract.

However, when it does occur, it may have marked significance (Table A III.1 and Figure A III.8).

APPENDIX IV
Antibiotics: parenteral and oral

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide drug dosage schedules that are complete and in accord with the standards accepted at the time of publication. However, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in these schedules is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

ORAL ANTIBIOTICS
Mark Martens, MD

Antibiotics have proven to be essential in the battle to prevent and treat postoperative infections. This is especially crucial for the obstetrician and gynecologist. The most frequently performed major surgical procedures in the United States are Cesarean section and hysterectomy. Because these surgeries are generally classified as clean-contaminated procedures, they not infrequently result in postoperative infections. Obstetricians and gynecologists have therefore become quite familiar with many of the intravenous antibiotics utilized in the treatment of these infections. However, with the recent emphasis on primary care, the obstetrician-gynecologist has needed to become well-versed in a variety of ambulatory infections such as sinusitis, bronchitis, skin and soft tissue infections, etc. and the oral antibiotics which are often utilized to treat them.

The number of new antibiotics and new classes of antimicrobials has rapidly proliferated in the past decade.

Principles of oral antibiotic therapy

(1) **The most site-specific agent should be utilized:**

Women, more so than men, may have several additional adverse effects from the disruption of the normal balance of bacteria in their bodies. While both men and women may demonstrate unwanted effects of antibiotics on intestinal flora such as diarrhea or pseudomembranous colitis, only women will have a disturbance of vaginal flora which may result in vaginitis or disruption of their gut flora which

may alter their absorption of contraceptive or postmenopausal hormones. Therefore, site-specificity, whether a result of the pharmokinetic properties of the antibiotic or the local application of topical agents, should be considered before the prescription of any anti microbial agent to a female patient.

(2) **The most narrow spectrum agent is preferred if effective for the diagnosed infection:**

Utilization of an agent of the most narrow spectrum is different from, but just as important, as

Table A IV.1 Parenteral antibiotics commonly used in obstetrics and gynecology

Antibiotic	***Dosage range****	***Route of administration***	***Dosing interval***
Category 1 Antibiotics			
First generation penicillins			
Beta lactamase-sensitive			
Crystalline G	1–4 Mu	IV	q4–6h
Benzathine syphilis:	2.4 Mu/d×1–3doses	0.6–1.2 Mu IM	q12h
Procaine			
Beta lactamase-resistant			
Methicillin	1–2g	IV or IM	q4–6h
Nafcillin NA	500mg-2g	IV or IM	q6h
Oxacillin	1–2g	IV or IM	q4–6h
Second generation penicillins			
Ampicillin	1–2g	IV	q4–6h
Third generation penicillins			
Ticarcillin	3g	IV	q4–6h
Fourth generation penicillins			
Mezlocillin	3g	IV	q4–6h
Piperacillin	3–4g	IV	q4–6h
Fifth generation penicillins/carbapenems			
Ampicillin and Sulbactam	1–2g	IV or IM	q6h
Ertapenem	1g	IV	qd
Imipenem and Cilastatin	500mg	IV	q6h

Meropenem	1g	IV	q8–12h
Piperacillin and Tazobactam	3.375–4.5g	IV	6–8h
Ticarcillin and Clavulanic acid	3.1g	IV	q6h
Cephalosporins			
First generation cephalosporins			
Cefazolin	1g	IV or IM	q8h
Cephalothin	500mg- 2g	IV	q8h
Cephapirin	0.5–2g	IV	q4–6h
Second generation cephalosporins			
Cefamandole	0.5–2g	IM or IV	q4–8h
Cefmetazole	2g	IV	q6–12h
Cefonicid	0.5–2g	IV or IM	q24h
Cefotetan	2g	IV or IM	q12h
Cefoxitin	2g	IV or IM	q6–8h
Cefuroxime	75-l.5g	IV or IM	q8h
Third generation cephalosporins			
Cefoperozone	1–2g	IV or IM	q6–12h
Cefotaxime	1–2g	IV or IM	q6–8h
Ceftizoxime	1–3g	IV or IM	q6–8h
Ceftriaxone	0.5–1g	IV or IM	q24h
gonorrhea:	bolus 250mg	IM	
Fourth generation cephalosporins			
Ceftazidine	1–2g	IV or IM	q8–12h
Vancomycin	15mg/kg	IV	q12h

Antibiotic	***Dosage range****	***Route of Administration***	***Dosing interval***
Category II Antibiotics			
Clindamycin PO_4	300–900mg	IV	q6–8h
Metronidazole	0.5g	IV	q6h
Ampicillin and Sulbactam	3g	IV or IM	q6h
Ticarcillin and Clavulanic acid	3.1g	4–6h	IV
Imipenem/Cilastatin	500mg	IV	q6h
Category III Antibiotics			

Trimethoprim-Sulfamethoxazole	3–5mg/kg	IV	6–12h
All penicillins are effective as Category III antibiotics (especially if therapy is coupled with the use of an aminoglycoside)			
Category IV Antibiotics			
Aminoglycosides			
Gentamicin	1 .7mg/kg	IV or IM	q8h
Netilmicin	2mg/kg	IV or IM	q8h
Fluoroquinolones			
Ciprofloxacin	400mg	IV	q12h
Trovofloxacin	300mg IV followed by 200mg	oral	

**For moderately severe infection*

site-specificity in antibiotic choices. Use of broad spectrum agents do have a very important place in the treatment of infections which are polymicrobial or are as yet undiagnosed and thus empirical. However, use of broad spectrum agents should not be utilized if more narrow spectrum agents are available and have been demonstrated to be effective against a specific pathogen. Unnecessary use of broad spectrum agents may lead to selection pressures for resistant species or strains of pathogens. Examples include the overuse of betalactam agents for urinary tract infections which has resulted in greater than 50% resistance of *E. coli* to inexpensive penicillin agents. This is despite the availability of more narrow spectrum agents specific for the most common etiologic agent *E. coli*. Also, the overuse of quinolone agents in the Far East for the treatment of *N. gonorrhoeae* has led to a more rapid distribution of resistance to quinolones in those areas of the world.

(3) **Oral antimicrobial agents should demonstrate in-vitro activity versus the offending agent and have been demonstrated effective in the treatment of the specific infectious disorder:**

Newly released agents should not be utilized, just because they are newer agents within a specific class. Newer is not necessarily better. Examples include the decreasing Gram-positive antimicrobial activity with the higher generations of cephalosporins, and some of the newer quinolones with respect to *Chlamydia trachomatis*.

(4) **The benefit of any specific agent should outweigh the risks of its use:**

Again, this recommendation is of greater importance in the treatment of infections in women. The primary example specific to women is antibiotic use in pregnancy. It must not only be safe for the women, but also for the fetus.

ANTIBIOTIC ANALYSIS

As new antibiotics are introduced, evaluation of whether or not a drug can penetrate an individual's

Table A IV.2 Orally and intramuscularly administered antibiotics commonly used in obstetrics and gynecology

Antibiotic	*Formulations*	*Daily Dosage*	*Dosing*
Ampicillin	250mg, 500mg caps	1–2g/day	q6h
Amoxicillin	250, 500mg caps	0.75–2g/day	q6–8h
Amoxicillin and Clavulanate	250/125mg tab; 500/125mg tab;	0.75–1.5g day 1	q8h
Azithromycin	250mg tab; 500mg day 1 then 250mg qd		
chlamydia: 1g bolus			
gonorrhea: 2g bolus			
Carbenicillin	382mg tab;	382–764mg	q6h
Cefaclor	250–500mg cap		q8h
Cefadroxil	500mg or 1g tab		q12h
Cefuroxime	125mg, 250mg	500mg cap	q12h
Cephalexin	250mg, 500mg caps;	250mg q6h or 500mg q 12h	
Cefixime	200, 400mg tab;	200mg q 12h or	400mg q24h
Clarithromycin	250, 500mg tab;	500–1000mg/day	q12h
Clindamycin	150, 300mg cap;	0.6–1.2g/day	q6h
Ciprofloxacin	100mg, 250mg;	500mg, 75mg tabs	0.2–1.5g/day
Dicloxacillin	125, 250, 500mg tab	125–250mg q6h	q6h
Doxycycline	50, 100mg tab or cap	200mg/day	q12h
Erythromycin	250mg	333mg 500mg tab	q6h
Ofloxacin	200, 300,400mg	400–800mg/day	q12h
Penicillin V	250, 500mg		q6–8h
Trovofloxacin	100, 200mg	200mg/day	q24h

clinical armamentarium can benefit from the following analysis:

(1) **Specific use designations:**

Is the antibiotic proposed as a 'drug-of-choice' for a given monoetiological disease or is it a drug with a singular or multicategory coverage?

(2) **Safety profile:**

Is it a safe drug for your patient?

(3) **Cost:**

In evaluating cost, cost of acquisition should not be confused with cost of utilization. The latter includes the costs of:

(a) acquisition
(b) administration
(c) adverse reactions
(d) failure
(e) toxicity monitoring

For example, gentamicin is an inexpensive antibiotic to purchase; however, it is an expensive antibiotic to use when cost of monitoring drug serum concentrations is included.

ORAL ANTIFUNGAL DRUGS

The principal uses of the azoles have been in the treatment of cutaneous, vaginal and oral mycotic infections. The azoles are active against the major endemic mycoses (histoplasmosis, blastomycosis and coccidioidomycosis) as well as most yeast and many filamentous fungi. Only itraconazole possesses *in vitro* activity against *Aspergillus* species.

Table A IV.3 Pharmacological comparison of azoles commonly used in ambulatory settings

Pharmacological properties	***Fluconazole***	***Itraconazole***	***Ketoconazole***
Absorption	Excellent; not affected by anti-acids	Requires acid pH decreased by antacids, H_2 blockers etc.	Requires acid pH decreased by antacids, H_2 blockers etc.
Distribution	Excellent in CSF, eye and other sites	Minimal in CSF, eye and other sites	Minimal in CSF, eye and other sites
Dosing frequency	Once daily	Once daily	Once daily
Excretion in Urine	>80%	Little	Little
formulation	100, 150mg	100mg	200mg
Metabolism	>80% renal excretion	Almost completely hepatic metabolism	Almost completely hepatic metabolism

Pharmacokinetics

Fluconazole

Owing to its water solubility, fluconazole is readily absorbed from the stomach and does not require gastric acidity for absorption (Table A IV.3). The drug is minimally bound and consequently achieves excellent penetration into cerebrospinal fluid (CSF) and other sites often inaccessible to drugs. Fluconazole is excreted unchanged primarily by the kidneys. The dosage must be reduced in patients with compromised renal function. For many forms of cryptococcus and candidiasis, fluconazole is the drug of choice.

Itraconazole and ketoconazole

Pharmokinetically, itraconazole and ketoconazole are similar. Both are poorly soluble in water, require low gastric pH for absorption, are highly protein bound and do not penetrate in CSF and intraocular fluids well. Itraconazole exhibits a saturation phenomenon. Doses above 200mg do not increase appreciably its serum level.

Adverse drug reactions

All of the azoles have the potential to cause or exacerbate hepatitis. The risk is most significant for ketoconazole (estimate at 1:15 000 courses of therapy). Serum liver function test should be done on patients receiving azole therapy greater than one week. Because of its superior efficacy and diminished toxicity, itraconazole has become the drug of choice in treating endemic mycosis. Some of the most serious problems encountered with the azoles are their potential drug interactions (Table A IV.4). Both ketoconazole and itraconazole interact with the antihistamines terfenadine (Seldane®), astemizole (Hismanal®) and cisapride Propulcid® and probably digoxin. Increased levels of these drugs may lead to ventricular arrhythmia. Phenytoin toxicity and bleeding secondary to increased warfarin levels may occur with fluconazole therapy. Cyclosporine toxicity has occurred with all three azoles. Concomitant administration of rifampin or isoniazid may lower serum azole concentration and induce a therapeutic failure.

THIRD WORLD USE OF ANTIBIOTICS WITHIN THE CONCEPT OF THE GAINESVILLE CLASSIFICATION

In many underprivileged countries, therapy is limited to oral administration. The following is an integration of orally administered antibiotics into the **Gainesville Classification**.

Triple therapy equivalence

It is possible to approach the four-category coverage required for the anaerobic progression of the

Table A IV.4 Dosing of fluconazole for candidiasis

Disease	***Dosing regimen***
Vulvovaginal candidiasis	150 mg—one dose
Oropharyngeal candidiasis in HIV positive individuals	100mg daily for 7–14 days
Candidal esophagitis	200 mg daily for 7–14 days
Candidal urinary tract infections	200 mg daily for 14 days

Gainesville Classification with oral antibiotics. Total coverage of the anaerobic progression would require:

(1) penicillin, amoxicillin, or ampicillin for Categories I and III;
(2) metronidazole or thiamphenicol for Category II; and
(3) a fluoroquinolone for Category IV.

An alternate approach would be trimethoprim/ sulfamethoxazole plus metronidazole. This combination would be less optimal. In the penicillin hypersensitive individual, use of erythromycin would be substituted for penicillin. The use of trimethoprim/sulfamethoxazole and a fluoroquinolone are restricted to the non-gravid individual. For a gravida, the closest approximation to a triple therapy would be amoxicillin/clavulanate (Augmentin®) plus metronidazole and a fluoroquinolone.

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